DOCUMENT RESUME

ED 348 604 CG 024 422

TITLE	Drug Abuse and Drug Abuse Research. The Third Triennial Report to Congress from the Secretary, Department of Health and Human Services.
INSTITUTION	National Inst. on Drug Abuse (DHHS/PHS), Rockville, Md.
REPORT NO	DHHS-Pub-NO-(ADM)91-1704
PUB DATE	91
NOTE	284p.
PUB TYPE	Reports - General (140)
EDRS PRICE	MF01/PC12 Plus Postage.
DESCRIPTORS	Cocaine; *Drug Abuse; Drug Rehabilitation; Drug Use; Incidence; Mental Disorders; Public Policy; Research Problems; Smoking; Trend Analysis; Use Studies

ABSTRACT

This report summarizes changes that have occurred in understanding of the health implications of the use and abuse of illegal and legal drugs as a result of research since 1986. It is noted that wherever possible, research findings have been summarized in non-technical language. Some technical material is included because of its basic importance and its relevance to the needs of specialists working on related problems and of those advising lawmakers and other civil authorities on public policy. These chapters are included: (1) "Nature and Extent of Drug Abuse in the United States" which discusses prevalence and consequences of drug use; (2) "Prevention Research" which discusses individual and environmental risk factors; (3) "Treatment Research" which summarizes treatment methods; (4) "Dual Diagnosis: Drug Abuse and Psychiatric Illness" which presents diagnostic issues and treatment strategies for dual disordered patients; (5) "AIDS (Acquired Immunodeficiency Syndrome) and Intravenous Drug Abuse"; (6) "Cocaine and Other Stimulants"; (7) "Marijuana and the Cannabinoids" which discusses health consequences; (8) "Phencyclidine (PCP) and Related Substances"; (9) "Heroin, Other Opiates, and the Immune Function" which focuses on recent research accomplishments; (10) "Sedatives and Anti-Anxiety Drugs"; (11) "Nicotine Dependence"; and (12) "Basic Research on Opioid Peptides and Receptors" which summarizes opioid advances. Bibliographies are included with each chapter. Statistics, tables, and graphs illustrate the report. Author and drug indexes are included. (ABL)

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DRUG ABUSE AND DRUG ABUSE RESEARCH

THE THIRD TRIENNIAL REPORT TO CONGRESS FROM THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES

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DRUG ABUSE
AND
DRUG ABUSE RESEARCH

The Third Triennial Report to Congress
from the Secretary, Department of Health and Human Services

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Alcohol, Drug Abuse,
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DHHS Publication No. (ADM)91-1704. Printed 1991.

Acknowledgments

Preparation of the Third Triennial Report on Drug Abuse and Drug Abuse Research to the Congress from the Secretary, Department of Health and Human Services, has been accomplished through the generous cooperation of many members of the scientific community. By making available their current research findings and recent work of other experts in the field of drug abuse, they have made it possible to include more up-to-date information than could otherwise have been presented.

Their contributions to the following chapters of the report are gratefully acknowledged:

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The contributions of those named and of the larger scientific community are gratefully acknowledged.

Mrs. Mary Louise Embrey and Dr. Christine R. Hartel at the National Institute on Drug Abuse had overall responsibility for preparation of the report. Mrs. Sally Breul assisted in administering and coordinating the preparation of the report, and Dr. Robert Petersen served as technical editor.

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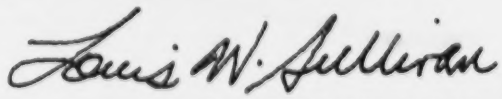
Preface

Today, no domestic issue captures the attention of the American public to the extent that drug abuse does. From the morning paper to the evening news, we are updated daily about the health and social problems that are caused by the use of dependence producing drugs. These drugs may be illegal ones like cocaine and marijuana or legal ones like nicotine and alcohol. There is no question of the pervasiveness of their use. One in three Americans have used an illicit drug at some time during their lives.

In the last 3 years, the U.S. Congress has authorized the spending of many millions of dollars to combat drug abuse problems in all their many aspects. The President, through the National Drug Control Strategy, has set an agenda for our Nation to become drug free. *Drug Abuse and Drug Abuse Research, The Third Triennial Report to Congress* summarizes the changes that have occurred in our understanding of the health implications of the use and abuse of illegal and legal drugs as a result of research since 1986. Research into these biological and social factors continues to prove how much we still have to learn. Though much remains to be done, the Triennial Report traces a record of research advances we can be proud of. It shows us that dependence producing drugs, even those with social or legal acceptability like nicotine, exact too high a price on our Nation's health and welfare. The research being conducted today will provide an even better knowledge base for the future. In turn, this expanded base will yield even greater improvements in our ability to prevent and treat drug abuse and dependence on both illegal and legal drugs.



Louis W. Sullivan, M.D.
Secretary
Department of Health and Human Services

EXECUTIVE SUMMARY

INTRODUCTION

The Secretary of the Department of Health and Human Services is required by law[1] to submit a triennial report to the Congress summarizing the extent of drug abuse in the United States, its health implications, and recent advances in the prevention and treatment of drug dependence. This is the third report in this series and emphasizes research developments that have occurred in the 3 years since the last triennial report was compiled. In writing the report, the National Institute on Drug Abuse (NIDA) has drawn upon experts knowledgeable in each of the areas covered. Wherever possible, research findings have been summarized in nontechnical language. However, the inherently technical nature of some areas makes this translation difficult. Some technical material has been included in the report because of its basic importance and its relevance to the needs of specialists working on related problems and of those advising

[1] Section 506(b) of the Public Health Service Act [USC 290aa-4].

lawmakers and other civil authorities on public policy.

NATURE AND EXTENT OF DRUG ABUSE IN THE UNITED STATES

Two major national surveys of drug abuse are ongoing; one deals with drug abuse in the general population, the other with the drug-using attitudes and behavior of high school seniors. Both surveys indicate that the rapid increase in drug abuse of the past 2 decades has been reversed. Abuse of almost all categories of drugs has decreased sharply from the epidemic levels of the 1970s. Most of the 72.5 million Americans who have used illicit drugs no longer do so. An important factor in this continuing reduction is the widening perception that illicit drugs are dangerous.

The number of Americans who used cocaine at all in the year prior to the survey was down from 12 million in 1985 to 8 million in 1988. However, the number of people who used cocaine frequently (once a week or more) did not decrease, but remained about the same. More than 1 in 10 (10.5 percent) Americans who reported using cocaine at all in the previous year had used it frequently.

The consequences of cocaine use are reflected in the data from hospital emergency rooms and in the data describing cocaine-related deaths. An analysis of data collected from emergency rooms between the second quarter of 1985 and the last quarter of 1988 indicates that there was a 354 percent increase in cocaine-related emergency room visits during that period. The number of cocaine-related emergency room visits remained stable during the first 3 quarters of 1989 and showed its first significant decrease (over 20 percent) during the last quarter of 1989. This decrease was maintained during the first quarter of 1990. Unfortunately, there has been no similar downturn in the number of cocaine-related deaths.

Other highlights include the following:

- Marijuana, the most commonly used illicit drug, has been used by a third of Americans. However, the percentage who reported using it in the month preceding the 1988 National Household Survey decreased to 5.9 percent from the 9 percent reporting current use 3 years before.

- Current marijuana use among 12- to 17-year-olds is at its lowest level in the past decade—6.4 percent compared with 16.7 percent in 1979 and 12 percent only 3 years ago.

- Marijuana continues to be an important "gateway" substance to other drug use. Thus, 3 out of 4 of those who have used it 200 or more times have also tried cocaine. Among those who never tried marijuana, fewer than 0.5 percent have used cocaine.

- In 1988, 12- to 17-year-olds were drinking and smoking less than this age group was in 1985. Approximately 25 percent of the group—down from 31 percent—had consumed alcohol in the month preceding the 1988 survey, and 11.8 percent were current smokers compared with 15.3 percent in the earlier survey.

- Over a third (35.2 percent) of young adults continue to smoke. However, the percentage of adults over 26 who smoke (29.8 percent) is only three-quarters as large as it was in 1974.

- Among high school seniors—a group at a pivotal point between adolescence and adulthood—there has been a marked change in attitudes toward drug use accompanied by a marked decline in use. Nearly 4 out of 5 seniors are now convinced that daily marijuana use poses "great risk," and 7 out of 10 feel that even occasional cocaine use poses a similar risk; 9 out of 10 high school seniors polled disapprove of any cocaine use.

- Of the over 260,000 drug abuse clients in treatment at the end of October 1987, New York State had nearly 70,000 and California had over 40,000; with 19 percent of the Nation's population, these 2 States had 42 percent of the Nation's drug abusers in treatment.

- Of those arrested for serious crimes in 14 major urban areas during the last third of 1988, 75 percent tested positive for illicit drugs.

PREVENTION RESEARCH

Effective prevention techniques depend heavily on an enhanced understanding of the multiple factors placing individuals at high risk of becoming drug dependent. As these factors—ranging from the genetic to the psychosocial—become better understood, more sophisticated techniques for early intervention are being developed. More recent approaches stress multiple levels of intervention involving the individual at risk, the family, and the community. Although it is often difficult to say which factors are pivotal in the individual case, the marked overall decline in illicit drug use over the past decade provides evidence that attitudes and behavior are shifting in response to altered perceptions of the personal risk and social acceptability of drug abuse. Some research developments critical to improved prevention include the following:

- Research on the heightened vulnerability among children of alcoholics to abuse alcohol is being extended to include children whose parents abuse other drugs.

- Studies on the relationship among low self-esteem, early antisocial and delinquent behavior, poor academic performance, family factors, alienation from family and school, and drug abuse are providing clues to better intervention approaches.

- Indepth investigation of why individuals reject drugs or discontinue their use despite early experimentation—can provide additional evidence of weak links in the causal chain—points at which preventive intervention is most likely to succeed.

- Prevention programs increasingly emphasize the development of interpersonal skills, enhanced self-perception, and the ability to resist peer pressure, as well as employ peer pressures to encourage remaining drug free.

- Techniques that have shown promise in preventing children and youth from becoming smokers are now being applied to a broader spectrum of drugs.

- Peer and community-wide prevention efforts are being used to reinforce drug prevention messages encountered in the school, the family, and other social contexts so as to ensure that drug-related messages from all sources are more consistent.

- Greater emphasis is being placed on targeting prevention efforts to persons or groups having high-risk biological, sociological, behavioral, or psychological factors.

TREATMENT RESEARCH

Although much research on which treatment and prevention are based involves controlled laboratory studies, its ultimate relevance is determined in the much less orderly context of the treatment setting. Although in practice the two approaches are frequently combined, treatment can be usefully divided into two categories: pharmacological or behavioral. The pharmacological approach prescribes medications to alter the user's physical state in ways that make it easier to stop abusing drugs. The behavioral approach aims at modifying the drug user's behavior through individual or group processes. The role of intravenous (IV) drug

abuse in spreading AIDS (see section on AIDS below) has given special urgency to treatment efforts to protect the health of IV drug abusers (IVDAs), as well as that of their sexual partners and children. Some highlights of recent developments include the following:

- By virtually every criterion used, there is good evidence that drug abuse significantly decreases following treatment. Other destructive personal and social effects of drug abuse, such as drug-related crime, suicidal behavior, psychiatric problems, incarceration, and unemployment, are also reduced.

- Drug abuse, like many other medical problems, is a chronic disorder in which recurrences are common and repeated periods of treatment are frequently required.

- There is evidence that a consistently firm response to nontherapeutic client behavior and strict enforcement of behavioral rules are important in achieving a successful treatment outcome in methadone maintenance programs.

- Buprenorphine, a pain killer combining methadone-like effects with the ability to block the effects of additional opioids, is being evaluated for use in the outpatient treatment of opioid abuse. Since the drug has limited commercial potential, NIDA will sponsor its further development as a drug abuse treatment modality.

- Clonidine, a drug used for controlling blood pressure, has potential for detoxifying opioid addicts and rendering a narcotic antagonist (naltrexone) more therapeutically effective.

- Use of contingency management—altering behavior by means of a clearly defined system of rewards and punishments—shows continuing promise in treating drug abusers and may be especially helpful with clients involved with the criminal justice system.

- A diversity of other treatment techniques and adjuncts, including classical conditioning techniques, variations on the therapeutic community, adjunctive psychiatric treatment, and the development of specific social, vocational, and job-seeking skills, have therapeutic value.

- Because clearly defined criteria for matching individuals and treatment approaches have yet to be developed, the availability of diverse treatment techniques is desirable if effective individual treatment is to be achieved.

DUAL DIAGNOSIS: DRUG ABUSE AND PSYCHIATRIC ILLNESS

Since drug dependence often occurs in individuals who have other psychiatric disorders as well, treating the combined problems simultaneously is important. Psychiatric diagnoses concurrent with drug dependence frequently include depression, alcoholism, organic impairment, schizophrenia, and character disorders. Patients with dual diagnoses are often difficult, expensive, and frustrating to treat. The two disorders usually interact in ways that make treatment of one but not the other futile. Yet, unfortunately, most drug abuse treatment facilities are not prepared to diagnose and treat existing psychiatric disorders in their clients. Because of differences in diagnostic criteria, there is significant variability from research study to research study in estimates of the frequency of dually diagnosed patients and in their reported characteristics. In addition, differences in gender, age, socioeconomic characteristics, and drug preferences may explain some of the variability. Additional research is needed to clarify these issues.

NIDA has funded an illustrative study of dually diagnosed male patients in a Veterans' Administration Medical Center setting. While these patients may not be representative of patients in all settings, they il-

lustrate the importance of considering possible psychiatric complications involved in treating drug abusers. Some highlights of this study include the following:

- Increased psychiatric symptoms are often associated with patterns of multiple drug use, especially the use of nonopiate drugs.
- Despite initial psychiatric findings of low levels of psychological symptoms, nearly half of the 11 stimulant abusers in the study were diagnosed as paranoid schizophrenic after 6 years of unremitting drug use.
- Depressant drug (benzodiazepines, alcohol, and barbiturates) users had predominantly depressive or anxiety disorders, but not psychoses. Suicidal feelings were common.
- In contrast to the stimulant and depressant drug users, the opiate-using group showed no significant psychiatric disorders other than sociopathy.
- Patients with the fewest psychiatric problems showed the greatest therapeutic improvement.
- Supplemental professional psychotherapy made little difference in therapeutic outcome with patients classified in a low-severity category of psychiatric problems. However, 6 months of professional psychotherapy significantly improved the therapeutic outcome for patients in a high-severity group.
- One method of improving treatment may be psychological assessment of drug abuse clients to permit more meaningful decisions in allocating scarce treatment resources. Additional research is needed in this area.

AIDS AND INTRAVENOUS DRUG ABUSE

Acquired immunodeficiency syndrome (AIDS), the end-stage illness associated with the human immunodeficiency virus (HIV) epidemic, is one of this century's most serious public health challenges. IV drug-associated transmission is a leading cause of the disease. IV drug abuse or sexual contact with IVDAs account for over 80 percent of AIDS cases in women, including those who infect their children with the disease. In New York City, 93 percent of heterosexually acquired infections are associated with having an IVDA for a sexual partner, and 80 percent of pediatric patients with AIDS have an IVDA parent. Current AIDS surveillance techniques may seriously underestimate the extent of HIV-associated mortality and morbidity among IVDAs, since there has been an unexplained increase in infectious disease deaths among IVDAs. Because of the seriousness of AIDS and its association with the use of shared "works" (paraphernalia used in injecting drugs intravenously), preventing this mode of transmission has achieved special urgency. This chapter reviews present knowledge in this area and prevention programs designed to reduce this source of HIV infection. Key findings include the following:

- The first wave of AIDS cases among IVDAs was noted as early as 1982 in New York City, and cases have now been reported from all 50 States, the District of Columbia, and Puerto Rico.
- Black and Hispanic IVDAs account for disproportionate numbers of the AIDS cases associated with IV drug use—over half are Black and nearly a third are of Hispanic origins.
- If HIV-associated mortality is adjusted to take into account excess deaths from infectious diseases in IVDAs, more than half (53 percent) of AIDS-related deaths in New York City would be associated with this form of drug use.

- HIV infection may also be responsible for the substantial increases in viral hepatitis among IVDAs because these cases too may be the result of HIV-impaired immune response.

- Studies done both here and abroad document the potential for rapid increases of HIV infection within the IVDA population. However, representative samples have not been studied, leaving the exact extent of HIV seroprevalence among IVDAs in doubt.

- Injecting drugs in so-called shooting galleries, where addicts gather to use drugs and often share works, is a common source of HIV infection.

- Cocaine injection either alone or in combination with heroin ("speedballing") has been associated with bacterial endocarditis, types A and B hepatitis, and most recently, HIV infection.

- Cocaine injection may add to the risk of sexual transmission of HIV infection both by increasing the likelihood of unprotected sex and by increasing the prevalence of sexually transmitted diseases, which are possible cofactors in HIV infection.

- IVDAs are frequently unaware of the multiple modes of HIV transmission and effective prevention measures.

- Treatment for IV drug abuse results in lower levels of HIV seroprevalence.

COCAINE AND OTHER STIMULANTS

The advent of "crack," a less expensive, smokable form of cocaine now widely available, has markedly changed the drug abuse picture throughout the United States. As noted, there have been sharp increases in cocaine-related deaths, drug-related emergency room admissions, and other complications of use. Other stimulant drugs such as amphetamine and chemically related compounds are also a source of concern. Most recently a smokable form of methamphetamine called "ice" has appeared in Hawaii, on the West Coast, and in the Midwest. Preliminary clinical reports indicate that the high produced by ice is more persistent (up to 24 hours) than that from crack and can result in acute psychotic episodes resembling paranoid schizophrenia. The popularity of such compounds is often difficult to predict. Earlier methamphetamine ("speed") epidemics abated as the drug's adverse effects became more widely known. Cocaine and other major stimulants, when used regularly, are profoundly dependence-producing, and their habitual use has serious toxic effects on users. The effects of cocaine use by pregnant women on their unborn children are also a serious concern. The socially disruptive and destructive effects of cocaine use, particularly in America's inner cities, are well documented. Although there have been some encouraging developments in treating cocaine dependency, there is still no specific treatment of demonstrated efficacy. Highlights of this chapter include the following:

- Contrary to earlier belief, high dose use of cocaine can be detected as long as 10 to 22 days after last use.

- As with other abused drugs, detection of cocaine in urine provides no indication of when—or whether—performance impairment occurred. Research correlating blood levels with performance decrements is needed.

- Additional animal evidence documents the fact that animals given unlimited access to cocaine will self-administer fatal doses.

- Cocaine's toxic effects affect the cardiovascular system, resulting in blockages in blood circulation, abnormal heart rhythms, and strokes. Blockage of blood to heart muscle is a significant risk in users even without evidence of coronary artery disease. Cocaine-

induced blood pressure increases can produce strokes.

- The increase in heart rate and blood pressure when marijuana and cocaine are used together is greater than when either is used alone and can be dangerously increased by concurrent exercise.

- Cocaine withdrawal is characterized by an initial crash or reactive depression, followed by up to several days of markedly increased need for sleep. The third withdrawal phase begins after the extended sleep period and is characterized by lethargy, intense cocaine craving, and an inability to experience pleasure.

- A drug known as "ecstasy" or sometimes "Adam" in street parlance has properties similar to those of LSD and cocaine and can cause fatal or near-fatal toxic reactions, possibly because of personal hypersensitivity or unusually high doses.

- Although a wide variety of treatments for cocaine abuse have been tried, none has been developed specifically for this drug. None of the therapeutic programs for opiate abuse appears to be effective in treating the intense craving characteristic of cocaine withdrawal or the high rate of relapse among these clients.

- No medication has been shown to prevent relapse to cocaine use. However, the antidepressant drug desipramine has shown promise in reducing cocaine use and drug craving and may attenuate positive effects experienced when cocaine is used. Other drugs used in treating psychiatric disorders have had only limited value in treating cocaine abusers and may prove ultimately ineffective.

- Detection and treatment of underlying psychiatric disorders in cocaine abusers may enhance treatment success.

- Detection and treatment of psychiatric disorders such as underlying depression, which may predispose individuals to use cocaine, may be effective means of preventing cocaine abuse.

- Since cocaine abuse by methadone maintenance program clients is an increasing problem, recent encouraging findings show buprenorphine, a drug used in treating opiate dependence, also reduces cocaine use in animals and humans.

MARIJUANA AND THE CANNABINOIDS

Although marijuana use has markedly decreased in virtually all segments of the population, it is still the most widely abused of the illicit drugs. There are still important unanswered questions about the effects of long-term use on mental, pulmonary, immune, and reproductive functioning. There is continued concern about the effects of marijuana use on physical, mental, and social development, particularly of children and adolescents. Although these effects cannot be studied in a controlled fashion, there is ample clinical basis for continuing to discourage use, especially by the young. Evidence of impairment of skilled psychomotor performance as a result of marijuana intoxication continues to mount. The combined effects of marijuana and alcohol used simultaneously are greater than when either is used alone. Except for the research associated with the introduction in 1987 of a new commercial form of THC (trademarked Dronabinol) for controlling nausea and vomiting resulting from cancer chemotherapy, there have been few additional studies of therapeutic uses of marijuana or its synthesized constituents. A brief overview of this chapter includes the following findings:

- Animal studies to determine the dependence liability of marijuana or its ingredients have generally found little evidence for its reinforcing effects. However, withdrawal effects have been found in monkeys, suggesting such

effects may play a role in continued human use.

- A study of 225 people who responded to a public service announcement directed at chronic adult marijuana users found that three-quarters of them reported adverse consequences of use.

- A combination of aversion and self management therapy for 4 weeks resulted in significant reductions in marijuana use among 22 clients who sought help in connection with their marijuana problem.

- There is some evidence of a cannabinoid receptor in the brain, but additional research is needed to clarify the nature of such a receptor.

- There is little new evidence of the role of marijuana in fetal development, although earlier research found congenital abnormalities and low birth weight associated with maternal use.

- Although the evidence of a marijuana effect on the intact human immune system has not been convincing, the increase in HIV infections raises the possibility that marijuana may have significant effects on already impaired immunity. This question remains to be resolved.

- Additional research on passive inhalation of marijuana smoke indicates it can produce detectable levels of marijuana metabolites in blood and urine, but that these are likely to be much below those resulting from actually smoking the drug.

- The correlation between performance decrements and blood levels of delta-9-THC, the active ingredient in marijuana, has generally not been very consistent. Single blood levels are unlikely to predict impairment or intoxication reliably, probably because of large individual differences in sensitivity to the drug. Continued research is important, however, since the issue of marijuana-related performance impairment is of legal interest.

PHENCYCLIDINE (PCP) AND RELATED SUBSTANCES

Phencyclidine (PCP) was originally developed as a general anesthetic in the 1960s, but later abandoned because patients often developed psychotic symptoms when emerging from its anesthetic effects. The popularity of PCP as a drug of abuse has waned in recent years as its possible adverse effects have become better known. However, for reasons that are unclear, it continues to be popular in some areas of the United States, notably the Nation's capital. Just why and under what circumstances the drug elicits psychotic behavior remain a mystery. It has also been implicated as a cause of violent behavior, although more recent evidence suggests this consequence is relatively uncommon. The possibility that it has adverse effects on the fetuses of PCP-abusing mothers has been raised, but it is difficult to tease out the role of PCP from that of other drugs that are also abused during pregnancy. Because PCP is related to a much wider range of potentially abused chemical analogs, research is continuing on this drug.

HEROIN, OTHER OPIATES, AND THE IMMUNE FUNCTION

Research conducted as early as the mid-1960s suggested that the immune functioning of opioid-dependent individuals is impaired. Although the role of opiates in affecting immune function and the implications of findings in this area continue to be unclear, this issue is of considerable potential importance. Compromised immune function resulting from opioid use may increase the risk of other intercurrent infections in this population, as well increasing their susceptibility to HIV infection. Illnesses such as viral hepatitis, venereal diseases, and of course HIV infec-

tion have profound public health implications not only for narcotic addicts, but for others with whom they have intimate contact. As already noted, individuals who inject drugs using nonsterile shared needles and other injection equipment are a particular source of public health concern. Because diminished immune response has such wide-ranging implications, this chapter provides an up-to-date review of the research in this important area and is primarily directed to the technically sophisticated reader.

SEDATIVES AND ANTI-ANXIETY AGENTS

Sedatives and other drugs that reduce anxiety are widely prescribed and frequently abused. They are used to treat such varied symptoms as anxiety, insomnia, muscle spasm, convulsions, and alcohol withdrawal. The bulk of evidence indicates these drugs are generally used appropriately and for the most part conservatively. They are prescribed more cautiously than they once were because of increasing physician awareness of their limitations and possible adverse effects, including possible dependence. These central nervous system depressants are sometimes used inappropriately for self-medicating anxiety and other emotional distress and are consumed less often for recreational reasons. According to DAWN data, one in six drug-related emergency room admissions is related to this drug group and is usually the result of an overdose. Over a third of those cases identified at emergency rooms as attempted suicides had used sedatives or anti-anxiety agents. Deaths associated with these substances usually occur when they are used in combination with alcohol. Clients of methadone treatment programs sometimes use diazepam and methadone in pursuit of a heroin-like euphoric effect. Highlights of this chapter include the following:

- Anti-anxiety and sedative drugs have been found to have reinforcing effects in both animal and human experiments and can produce physical dependence; that is, withdrawal symptoms can result after prolonged administration.
- Dose and duration of drug use are important for developing tolerance and physical dependence on these drugs.
- Symptoms that can occur when chronic use of these drugs is discontinued include anxiety, insomnia, agitation, irritability, loss of appetite, tremor, muscle twitching, nausea, vomiting, heightened sensitivity to light and sound, and psychological disturbances, sometimes including hallucinations and feelings of depersonalization.
- Prolonged use at therapeutic doses can cause withdrawal symptoms.
- Rebound insomnia following drug discontinuance can cause individuals to resume use of sedative drugs.
- The faster the drug is eliminated from the body after use is discontinued, the more severe the withdrawal symptoms are likely to be.

NICOTINE DEPENDENCE

Tobacco has been consumed for several hundred years, and the dependence-producing qualities of nicotine were suspected long before they were systematically investigated. Adverse health consequences were also attributed to the drug's use before they were scientifically explored. Since the 1970s the biological basis for tobacco use and nicotine's dependence-producing effects has been the subject of more intense research study. Data from national surveys of drug use also make clear that there is an association between the use of tobacco and other forms of drug dependence. This chapter summarizes recent research confirming nicotine's appropriate classification as a dependence-producing drug and examines some of the more recent efforts at preventing and treating the physical and psychological dependence that so often results from tobacco use. Highlights include the following:

- The effects of smoking by pregnant women on their pregnancy and the developing fetus are now well documented: diminished average birth weight, reduced head size, more frequent miscarriages, and other birth complications.

- When the effects of tobacco use by pregnant women on their offspring were compared with those of alcohol, marijuana, and other abused drugs, a recent study found the most pronounced effects related to nicotine.

- Maternal smoking was also found to be related to lower developmental scores and altered auditory response in infants even a year after birth.

- There is now evidence from research on animals that radioactively labeled nicotine binds to specific brain sites associated with other drug dependencies.

- Women smokers puff cigarettes more frequently while menstruating, suggesting that cigarette smoking is complexly related to hormone function in women.

- Recently improved methods of detecting nicotine metabolites (transformed products of nicotine ingestion) provide a more reliable objective means for measuring both active (smoking) as well as passive exposure to tobacco smoke.

- Smokers who metabolize nicotine more slowly (that is, in whom nicotine is more slowly eliminated from the body) smoke less frequently.

- Potential health benefits of smoking less or smoking lower nicotine cigarettes are sharply reduced because smokers unconsciously adjust their smoking behavior to maintain their usual blood levels of nicotine. Heavy smokers do this more than light smokers.

- Nicotine withdrawal symptoms, the evidence of physical dependence on nicotine, are directly related to the amounts consumed before stopping use.

- Withdrawal symptoms such as insomnia, increased weight, anxiety, and restlessness when smoking is discontinued may be partially attributable to elevated caffeine levels resulting from changes in caffeine metabolism after smoking cessation.

- There is now evidence that children and adolescents also develop physical dependence on nicotine, making smoking difficult to stop once begun.

- Cigarette smokers weigh less than nonsmokers of the same age, and many smokers who quit smoking gain weight. Heavy smokers gain more weight after they stop smoking than light smokers.

- Nicotine gum is most helpful to moderately heavy smokers trying to discontinue smoking. Heavy smokers have difficulty extracting sufficient nicotine from the currently available dosage of the gum.

- Use of a pocket-sized computer to assist smokers in reducing their cigarette smoking has been helpful.

- Systematic social support, particularly the support of a significant person in the ex-smoker's life, plays an important role in remaining abstinent.

- Alternative means of delivering nicotine such as nasal sprays, skin patches, and use of a nicotine vapor inhaler may help reduce smoking.

- Children and adolescents in grades 2 to 12 in one urban public school system greatly overestimated the extent of adult and peer smoking

and had a poor understanding of how nicotine dependence develops. They also underestimated the negative attitudes of their peers toward smoking. Education concerning these aspects may enhance smoking prevention efforts.

BASIC RESEARCH ON OPIOID PEPTIDES AND RECEPTORS

Basic research on the mechanisms underlying drug dependence has become an important and exciting area of scientific research. In little more than 15 years, researchers have progressed from an initial awareness of naturally occurring opiate-like substances—called endorphins—in the brain and other parts of the body to an understanding of their chemical structure, their distribution, and the ways in which they are synthesized and metabolized. These substances and the brain receptors with which they interact play fundamental roles in controlling sensitivity to pain, responsiveness to stress, motor coordination, learning, and memory and are basically involved in the reward mechanisms central to the abuse of drugs. These naturally occurring substances act on various receptors, sometimes called "second messengers" (the substances themselves are referred to as "first messengers"), whose functions are less well understood. Research on the families of opiate receptors has been a major emphasis of the past 3 years. Better understanding of how the first and second messengers function in the brain may ultimately provide ways to detect biological vulnerability to drugs, ways of preventing or treating drug abuse more effectively, and ways of developing effective pain-relieving drugs with little or no abuse potential. This chapter outlines recent developments in this sophisticated area of neurochemical and neurophysiological research. Although understanding the details requires considerable technical knowledge, some of the highlights of this area are of more general interest:

- Understanding this complex brain reward and neurotransmitter system requires the study of the dynamics of the system, not simply the quantification of transmitter substances.

- Cloning, the exact reproduction of the enzymes involved in the biosynthesis of the opioid peptides, is an important step in understanding endorphins and their functions. Research on these functions has lagged behind that characterizing the endorphins themselves.

- A question that has intrigued researchers since the discovery of the endorphins is what happens to the natural production of these substances when someone takes heroin or other artificial opiates. Unlike other bodily systems, there is no evidence that the body stops or cuts down on production of these naturally occurring opiates when exogenous opiates are taken. Present evidence suggests that under these circumstances, the brain metabolizes endorphins of different potencies. The resulting alteration in brain metabolism may be responsible for the withdrawal symptoms the addict experiences.

- It is now apparent that a one-to-one correspondence between the multiple opioid peptide families (the groups of endorphins) and the multiple opioid receptors does not exist. Products from a given peptide group interact with more than one opioid receptor and a given receptor, can receive signals from more than one family.

- The ultimate challenge in this research area is determining the basis for the large individual differences in susceptibility to becoming drug dependent.

NATURE AND EXTENT OF DRUG ABUSE IN THE UNITED STATES

INTRODUCTION

Drug abuse has become a major problem in the United States, affecting multiple facets of American life. To understand the nature and extent of this national problem and its wide ranging implications, it is necessary to analyze many sources of data on the incidence, prevalence, morbidity, mortality, and other adverse social consequences associated with drug abuse. These data are derived from large-scale national surveys as well as small-scale epidemiological studies and investigations. Many of these surveys are ongoing or are conducted periodically and can, therefore, provide evidence of trends. Research is not limited to estimating the magnitude of the problem, but also includes examining variables which may define and explain behavior patterns and the sociodemographic characteristics of drug abusers. To meet the goals of drug abuse prevention, demand reduction, and treatment, it is crucial to know which subgroups of our population are at greatest risk of abusing drugs.

Characteristics of high-risk subgroups may differ by drug type and certain types of drug abuse may predispose users to specific adverse health consequences (Kozel and Adams 1986). The consequences of drug abuse are dynamic and dependent on such factors as the specific drug(s) used, modes of use, the frequency, intensity and duration of use. Ongoing data collection systems monitor these consequences and drug abuse trends and are essential tools in developing public health strategies for intervention and control.

The primary data source for determining the incidence and prevalence of drug abuse in the United States among the entire population aged 12 years and older is the National Household Survey on Drug Abuse (NIDA 1989a). The first of these nationwide surveys was done in 1971, and they have been sponsored by NIDA since 1974. The Household Survey is conducted every 2 to 3 years. The latest survey, the ninth in the series, was done in 1988. The next national survey is planned for 1990. Although this national prevalence survey omits small segments of the population not living in household units that may have high rates of drug use (e.g., prison inmates and the homeless), it remains the single most important measure of drug abuse prevalence and of national drug abuse trends in the total population. The methodology has been comparable for all of the surveys: respondents are interviewed in their homes by trained interviewers using a combination of interviewer-administered and self-administered answer sheets and standardized methods to maximize response validity. All data are confidential and anonymous. Respondents are randomly selected within age categories from a multistage national probability sample representative of 98 percent of the population 12 years of age or older.

A second large-scale epidemiological survey of drug use, the Monitoring the Future Study, was initiated in 1975 through a grant awarded by NIDA to the University of Michigan's Institute for Social Research (Johnston et al. 1989). This survey measures drug abuse prevalence among high school seniors and graduates, as well as college students in the age range from 19 to 30. It is conducted annually in order to monitor trends in drug abuse and drug-related attitudes in adolescents and young adults at important transitional points in their lives.

A major source of data on the health consequences of drug abuse is the Drug Abuse Warning Network (DAWN) (NIDA 1989b). DAWN is a large-scale, ongoing drug abuse data collection system sponsored by NIDA. DAWN data are obtained from a nonrandom sample of hospital emergency rooms and medical examiners primarily located in large metropolitan areas.[1] DAWN collects information about drug abuse related to those seeking hospital emergency room treatment and to deaths reported by medical examiners.

Data from drug abuse treatment facilities are also used to measure the consequences of drug abuse. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) and NIDA jointly sponsor the National Drug and Alcoholism Treatment Unit Survey (NDATUS) (NIDA 1989c) and the State Alcohol and Drug Abuse Profile (SADAP) (Butynski et al. 1989), two basic sources of national treatment data.

NDATUS surveys both publicly and privately funded facilities, with more complete coverage of public facilities. SADAP surveys primarily facilities which received at least some funds administered by the State.

Because of the dynamic nature of drug abuse and the often localized occurrence of drug abuse patterns, it is also important to supplement national data bases with epidemiologic surveillance and field studies to get a more complete picture of the nature and extent of drug abuse. These methods can identify and provide data on geographic areas and subpopulations with unique drug abuse patterns.

DRUG ABUSE PREVALENCE

During the past two decades, drug abuse in the U.S. has increased dramatically. Based on surveys

done in the 1970s we estimate that in the early 1960s less than 5 percent of the population had had any experience with illicit drugs (including the use of marijuana, hashish, cocaine, inhalants, hallucinogens, heroin, and nonmedical use of psychotherapeutic drugs) (NIDA 1979).[2] But by the early 1970s, that percentage had doubled to over 10 percent, primarily because of use by those under age 25 (NIDA to be published). By 1974, over half of young adults (ages 18-25) and over one-fifth of those in the 12-17 age group had tried illicit drugs. As this cohort of young people grew older and as younger cohorts continued to experiment with these drugs, the percentage of the population who had used illicit drugs one or more times (lifetime prevalence) increased rapidly. By 1988, an estimated 36.6 percent (72.5 million) of Americans age 12 and older had used these substances. Experience with illicit drugs is no longer restricted to youth and young adults. Nearly a quarter (23 percent) of adults age 35 and older had tried illicit drugs by 1988 (NIDA, National Household Survey, 1988).

Although experimentation with illicit drugs is widespread, most of the 72.5 million Americans who have ever tried illicit drugs no longer use them. In 1988, 14.1 percent of the population age 12 and older (28 million people), had used illicit drugs during the past year. Furthermore, 7.3 percent of the population age 12 and older (or 14.5 million people) were current drug users (i.e. had used an illicit substance in the past month). Those using drugs in the previous year represented less than half of those who had ever tried them and current users represented one-fifth of lifetime users. More recent users are the primary concern since they are at the highest risk of suffering consequences of drug abuse.

There have been encouraging recent downward trends in drug abuse prevalence. The aging of cohorts with high rates of youthful use has inevitably resulted in an increase in lifetime prevalence rates (these estimates are, of course, cumulative), but lifetime prevalence among younger groups and current prevalence for all age groups has declined since 1979. Today's youth are much less likely to use drugs than the youth of 1979 were. Between 1979, the peak year for drug abuse prevalence, and 1988, the lifetime use of marijuana, hallucinogens, cocaine, cigarettes, and alcohol by those under age 25 has decreased significantly. Among high school seniors, similar decreases have occurred in lifetime as well as current drug use. In the total population as measured by the Household Survey, current use of illicit drugs has continued to decrease with particularly large decreases between 1985 and 1988. Illicit drug use which involved 12.1 percent of the population age 12 and over (23 million) in 1985 decreased to 7.3 percent (14.5 million) in 1988. Table 1 shows current use rates by age group for selected drugs and current drug use rates for high school seniors over time. Although cocaine use is an exception to the general pattern of decline observed for drug use since the early 1980s, the percentage of seniors reporting cocaine use during the past month significantly declined between 1985 and 1989. This is consistent with the trend seen in the household population in which prevalence declined from 5.8 million users in 1985 to 2.9 million users in 1988. The declines in drug use that have occurred since 1979 have occurred during a period of stable or increasing availability of illegal drugs, as suggested by the data in table 2. One factor that seems to have played a role in drug use reduction is an increasing awareness that use of illicit drugs is dangerous. For example, 31 percent of youth ages 12-17 in 1985 reported that there was "great risk" in trying cocaine, whereas in 1988, 53 percent believed this. Similar increases in perceived risk occurred for other age groups and for other illicit drugs (table 3).

Because polydrug abuse (use of several different drugs concurrently) is common, focusing on a single drug of abuse cannot provide a complete picture of the nature and extent of drug abuse. However, studying the problem in terms of prevalence of use of each of the major drugs does provide a way of looking more closely at patterns of use and differences among population groups. Table 4 shows current prevalence rates by drug type and age of users for 1988. The following drug-by-drug analysis highlights variations

TABLE 1. Trends in Past Month Use of Selected Drugs: United States, 1974–1988

	HOUSEHOLD POPULATION					
	1974	1977	1979	1982	1985	1988
(Unweighted N)	(4,022)	(4,594)	(7,224)	(5,624)	(8,038)	(8,814)
Age 12–17						
Any illicit use[1]	NA	NA	17.6	12.7	14.9	9.2
Marijuana	12.0	16.6	16.7	11.5	12.0	6.4
Cocaine	1.0	0.8	1.4	1.6	1.5	1.1
Hallucinogens	1.3	1.6	2.2	1.4	1.2	0.8
Age 18–25						
Any illicit use[1]	NA	NA	37.1	30.4	25.7	17.8
Marijuana	25.2	27.4	15.5	27.4	21.8	35.4
Cocaine	3.1	3.7	9.3	6.8	7.6	4.5
Hallucinogens	2.5	2.0	4.4	1.7	1.9	1.9
Age 26 and Older						
Any illicit use[1]	NA	NA	6.5	7.5	8.5	4.9
Marijuana	2.0	3.3	6.0	6.5	6.1	3.9
Cocaine	*	*	0.9	1.2	2.0	0.9
Hallucinogens	*	*	*	*	*	*
		HIGH SCHOOL SENIORS				
		1977	1979	1982	1985	1988
(Unweighted N)		(17,100)	(15,500)	(17,700)	(16,000)	(16,300)
Any Illicit Use[1]		NA	NA	32.5	29.7	21.3
Marijuana		35.4	36.5	28.5	25.7	18.0
Cocaine		2.9	5.7	5.0	6.7	3.4
Hallucinogens		NA	5.3	4.1	3.8	2.3

[1]Includes use of marijuana, hashish, inhalants (except in 1982), hallucinogens, cocaine, heroin, and nonmedical use of stimulants, sedatives, tranquilizers, or analgesics

*Low precision-no estimate made; these estimates are usually very small.

Source: NDA, National Household Survey on Drug Abuse (1988) and Monitoring the Future Study (1988)

TABLE 2. Trends in Perceived Availability of Drugs and Perceived Harmfulness of Using Drugs Among High School Seniors, United States, 1977–1988

	HIGH SCHOOL SENIORS					
	1977	1979	1982	19885	1988	1988
(Approximately Unweighted N)		(3,052)	(3,172)	(3,557)	(3,250)	(3,231)
Perceived Availability[1]						
Marijuana		87.9	90.1	88.5	85.5	85.0
Cocaine		33.0	45.5	47.4	48.9	55.0
Perceived Harmfulness[2]						
Marijuana		9.5	9.4	11.5	14.8	19.0
Cocaine		35.6	31.5	32.8	51.2	34.0

[1]Data given are the percent saying drug would be fairly easy or very easy for them to get.
[2]Data given are the percent saying there is a great risk in trying the drug once or twice.

Source: NIDA, Monitoring The Future Study, 1988

in drug use prevalence rates across different population groups.

Marijuana Use

Marijuana remains the most commonly used illicit drug in the United States. A third of Americans—almost 66 million people—have tried it one or more times. Four million youth (12-17), 17 million young adults (18-25), and over 45 million adults age 26 and older have used marijuana. Marijuana has been called a "gateway drug" because its use is associated with the use of other drugs. For example, lifetime cocaine use is rare (less than half of 1 percent) among people who have never used marijuana and the likelihood of having used cocaine increases as marijuana use increases. Among those who have used marijuana 200 or more times in their life, 77.4 percent have tried cocaine.

In 1988, 5.9 percent (11.6 million) of the population age 12 and older in 1988 were current marijuana users (that is, had used it in the past month). Current use was higher for males (7.9 percent), for young adults ages 18-25 (15.5 percent), for the unemployed (14.8 percent), and for those living in large (1980 census 1,000,000 or more) metropolitan areas (6.9 percent). Of the 21.1 million people who had used marijuana in the previous year, almost one-third, or 6.6 million, used it once a week or more.

Cocaine Use

The 1988 survey found 10.7 percent or 21.2 million people age 12 or over had used cocaine at some point. The overall rate of current use was 1.5 percent, with males (2.0 percent), those aged 18-25 (4.5 percent), the unemployed (4.6 percent), and minorities (2.0 percent for blacks and 2.6 percent for Hispanics) having higher rates of use. Among the 8.2 million who had used cocaine in the past year, 10.5 percent used it once a week or more, compared to 5.3 percent of the users in 1985 who were weekly users. Thus, despite

TABLE 3. Trends in Perceived Harmfulness of Drugs by Age, 1985 and 1988

		PERCENTAGE SAYING "GREAT RISK"	
	AGE GROUP	1985	1988
Smoke Marijuana Occasionally	12–17	37.2	44.1
	18–25	20.7	31.1
	26–34	24.0	31.1
	35+	54.3	62.2
Try PCP	12–17	56.9	63.3
	18–25	66.6	73.2
	26–34	73.5	78.2
	35+	83.0	88.0
Try Cocaine	12–17	30.7	52.8
	18–25	34.3	56.5
	26–34	41.4	59.9
	35+	70.2	82.7
Try Heroin	12–17	57.4	61.1
	18–25	63.7	69.8
	26–34	58.9	67.1
	35+	67.5	73.9

the decrease in users that occurred between 1985 and 1988, there was no decrease in the number of heavy users. Though not statistically significant, there has in fact been an increase in the estimated number of heavy users.

While lifetime prevalence of cocaine use remained stable for whites and blacks between 1985 and 1988, a significant increase occurred among Hispanics, from 7.3 percent to 11.0 percent. The increase among Hispanics occurred in all regions of the country, in metropolitan and nonmetropolitan areas, and for both sexes. However, it did not occur among Hispanic youth ages 12-17.

Approximately 1.3 percent of the population age 12 and over have used crack at some time in their life, a half of 1 percent in the past year. This translates to about one million who had used crack in 1988.

Heroin Use

Household surveys do not adequately measure the prevalence of heroin use and are believed to result in significant underestimates, particularly for current use. Nevertheless, 1988 Household Survey data show that 1.9 million Americans (1.0 percent) have tried heroin. Rates of lifetime use were highest for males (1.3 percent) and for blacks (2.3 percent). Under a NIDA contract in progress, an estimate of the number of

TABLE 4. Prevalence of Drug Use in the Past Month by Age Group, 1988

DRUG	AGE GROUP				
	12-17	18-25	26-34	35+	All Ages
(Unweighted N)	(3,095)	(1,505)	(1,987)	(2,227)	(8,814)
Any illicit use[1]	9.2	17.8	13.0	2.1	7.3
Marijuana and hashish	6.4	15.5	10.8	1.4	5.9
Inhalants	2.0	1.7	0.6	*	0.6
Hallucinogens	0.8	1.9	*	*	0.4
Cocaine	1.1	4.5	2.6	0.4	1.5
Crack	0.3	0.8	0.3	*	0.2
Nonmedical use of any psychotherapeutic	2.4	3.8	2.7	0.7	1.7
Stimulants	1.2	2.4	0.9	0.4	0.9
Sedatives	0.6	0.9	0.6	0.2	0.4
Tranquilizers	0.2	1.0	1.2	*	0.6
Analgesics	0.9	1.5	0.9	*	0.6
Cigarettes	11.8	35.2	37.1	27.3	28.8
Smokeless Tobacco	3.6	6.3	2.8	3.1	3.6
Alcohol	25.2	65.3	64.2	51.5	53.4

[1]Includes use of marijuana, hashish, inhalants, hallucinogens, cocaine, heroin, and nonmedical use of stimulants, sedatives, tranquilizers, or analgesics in the past month.

*Low precision—no estimate made; these estimates are usually very small.

Source: NIDA, 1988 National Household Survey on Drug Abuse

current heroin addicts is being developed using mathematical modeling. Previous modeling methods estimated there were about 500,000 heroin addicts in 1982 (Brodsky 1985).

Intravenous Drug Use

The nature and extent of intravenous (IV) drug use in the U.S. are critical concerns because it is a primary mode of transmission for the HIV virus. While accurate data on the number of intravenous (IV) drug users in the U.S. do not exist, researchers have speculated that the size of this population is between 1 million and 1.5 million. An estimate compiled from "best guess" estimates obtained from individual State Alcohol and Drug Abuse Agencies was 1.3 million, with New York, California, and Pennsylvania reporting the largest numbers (Butynski et al. 1989). Data from NIDA's 1985 client treatment data system (NIDA 1987), as well as more recent DAWN data, indicate that most IV drug use involves injecting

heroin, cocaine, or amphetamines. Estimates from the 1988 Household Survey, which are conservative, indicate that 1.3 percent of the population age 12 and older, or 2.5 million people, have used one or more of these drugs intravenously at some time in their lives. Seventy-three percent of these IV users were male, and blacks had higher rates of use (2.0 percent) than whites (1.2 percent) or Hispanics (1.3 percent). Past year IV use occurred mainly among 18-34-year-olds.

Other Illicit Drug Use

Hallucinogens, which first gained prominence during the 1960s, include such drugs as LSD, PCP, mescaline, peyote, and MDMA ("Ecstasy"). Lifetime prevalence of these drugs is highest among 26-34-year-olds (17.7 percent) and current prevalence is highest among 18-25-year-olds (1.9 percent).

Nine percent of youth have experimented with inhalants, but current use is rare. Only 2 percent of youth and young adults, and less than one-half of 1 percent of older adults are current inhalant users.

Current nonmedical use of psychotherapeutic drugs (sedatives, tranquilizers, stimulants, and analgesics) decreased from 3.2 percent in 1985 to less than 2 percent in 1988. Current use was slightly higher for females (2.0 percent) than males (1.4 percent), and was highest among 18-25-year-olds (3.8 percent). Stimulants, which include methamphetamine, were the most commonly used category of psychotherapeutic drugs among current users (NIDA 1989a).

Use of Alcohol and Tobacco

Use of alcohol and tobacco products can have adverse health consequences regardless of whether or not illicit drugs are also used. Use prevalence of these legal substances is also relevant to the epidemiology of illicit drug use since users of alcohol and tobacco are far more likely to use illicit drugs than are nonusers. Alcohol is also commonly used in combination with illicit drugs. For example, 13 percent of current tobacco smokers surveyed in 1988 were also current marijuana users; however, only 3 percent of nonsmokers used marijuana. For alcohol, 10 percent of current drinkers were current marijuana users, compared to only 1 percent of nondrinkers. Although alcohol use is illegal for youths age 12-17, half of this group surveyed in 1988 had used alcohol at some point and 25 percent were current drinkers. However, prevalence has decreased since 1985 when 56 percent of youths had tried it and nearly a third (31 percent) were current drinkers. Current smoking rates for youth also decreased—from 15.3 percent in 1985 to 11.8 percent in 1988. Lifetime prevalence of smokeless tobacco was 14.9 percent of the population age 12 and older, or 29.4 million people in 1988. Most users (87 percent) were male. Less than one percent (only 0.6 percent) of females were current users of smokeless tobacco compared to 6.8 percent of males.

CONSEQUENCES OF DRUG ABUSE

Despite the encouraging downward use trends in the 1980s, some adverse health consequences connected to substance abuse increased. Hospitals consistently reporting to the Drug Abuse Warning Network (DAWN), reported that the number of people admitted to emergency rooms following cocaine use increased over five-fold in the period from 1984 to 1988—from 8,831 to 46,020. Fortunately, the number of emergency room mentions of cocaine leveled off during the first three quarters of 1989 and actually decreased 20 during the last quarter of that year (NIDA, DAWN, 1990). Much of the increase between 1985 and 1988 involved smoking cocaine, primarily in the form of crack. Cocaine smoking cases increased from 549 in 1984 to 15,306 in 1988. The number of DAWN reported deaths following cocaine use more than tripled over the same time period. Table 5 displays recent trends (from consistently reporting facilities) in emergency room mentions and drug abuse deaths for heroin, cocaine, and marijuana. In addition

TABLE 5. Trends in Emergency Room (ER) and Medical Examiner (ME) Mentions of Heroin and Cocaine, and Emergency Room Mentions of Marijuana: United States, 1984–1988

	Heroin		Cocaine		Marijuana	
	Mentions		Mentions		Mentions	
	ER	ME**	ER	ME**	ER	ME**
1984	11,437	1,088	8,831	628	3,542	*
1985	13,131	1,391	11,099	717	4,025	*
1986	14,209	1,644	20,383	1,223	4,779	*
1987	15,359	1,604	34,661	1,725	7,418	*
1988	16,815	1,732	46,020	2,163	8,232	*

* Less than one half of 1 percent.

** Does not include New York City metropolitan area.

Note: Based on consistently reporting ERS with at least 90 percent reporting in the first 12 months, the second 12 months, and the last 36 months.

Source: National Institute on Drug Abuse, Drug Abuse Warning Network (DAWN) historical data files as of March 1989 (ER data) and June 1989 (ME data)

to increases noted for these drugs, amphetamines and hallucinogens mentions in connection with emergency room visits have also increased since 1984. Some of the factors contributing to the increases in health consequences noted during this period of declining drug abuse prevalence are: increases in frequency of use among those who continue to use, higher drug dosages, greater purity of street drugs, more hazardous routes of administration (e.g., an increase in smoking and injecting cocaine), the combined use of drugs, and complications associated with long-term use and aging of the user.

Data on the characteristics of people suffering the negative consequences of drug abuse help identify those segments of the population most severely affected by drug abuse. These data can also identify the patterns of use and drugs that are most likely to result in adverse effects. For example, while marijuana is used by more people than any other illicit drug, the majority of emergency room visits and treatment admissions for drug abuse are related to cocaine and heroin.

Drug Abuse Related Deaths

The majority of 1988 drug-related deaths reported to DAWN involved either cocaine (49 percent) or heroin (37 percent). Many of these deaths involved these drugs used in combination, commonly called "speedballing." Alcohol was a factor in 38 percent of deaths reported to DAWN, although alcohol deaths are not included in the DAWN data if other drugs were not involved. Males accounted for 80 percent of the cocaine-related deaths, 83 percent of the heroin-related deaths, and 73 percent of all deaths reported to DAWN. Blacks accounted for 41 percent of cocaine-related deaths and 32 percent of heroin-related deaths, even though they compose only 16 percent of the U.S. population in large metropolitan areas (estimated from the 1988 National Household Survey on Drug Abuse data file), which the DAWN data reflect. Half of the

heroin deaths and almost half of the cocaine deaths occurred among 30-39-year-olds. Cocaine deaths were more likely to involve people under age 30 than were heroin deaths.

The number of cocaine-related deaths reported to DAWN may well be an underestimate. Mittleman and Wetli (1987) reanalyzed autopsy material from 24 patients who were presumed to have suffered sudden natural deaths. Eleven of these patients were found to have cocaine in their blood. This does not necessarily mean that cocaine was the cause of death in any of these cases, but it does indicate the need for more careful analyses of the cause of death.

Emergency Room Episodes

Tables 6 and 7 show the most frequently mentioned drugs in DAWN emergency room episodes. These episodes included suicide attempts, which comprised 28 percent of all DAWN episodes in 1988. Episodes can involve the mention of two or more drugs, and thus be counted as two or more separate drug mentions. Over one-third of all the drug-related episodes in 1988 involved cocaine. Males accounted for 56 percent of all drug episodes, but 67 percent of cocaine mentions, 70 percent of heroin mentions, 75 percent of PCP mentions, and 72 percent of marijuana/hashish mentions (most of which involved other drugs).

Females, on the other hand, accounted for 53 percent of diazepam episodes, 70 percent of alprazolam episodes, and 65 percent of amitriptyline episodes. These and many other drugs are more likely to be used by females in suicide attempts. Overall, suicide was the drug use motive in 43 percent of the episodes involving female patients compared to only 17 percent of the E.R. episodes involving males. Many of the drugs frequently reported to DAWN emergency rooms are primarily mentioned in suicide attempts, including alprazolam (70 percent suicide attempts), aspirin (82 percent), acetaminophen (80 percent), and ibuprofen (81 percent).

TABLE 6. Drugs Mentioned Most Frequently in DAWN Emergency Room Episodes in 1988

Drug Name	Number of Mentions	Percent of Total Episodes
Cocaine	62,141	38.8
Alcohol-in-Combination	46,588	29.1
Heroin/Morphine	20,599	12.9
Marijuana/Hashish	10,722	6.7
PCP	8,403	5.3
Acetaminophen	6,426	4.0
Diazepam	6,082	3.8
Aspirin	5,544	3.5
Ibuprofen	3,878	2.4
Alprazolam	3,846	2.4
Methamphetamine	3,030	1.9

Source: National Institute on Drug Abuse, Drug Abuse Warning Network (DAWN) historical data files as of May 1989

TABLE 7. Most Frequently Mentioned Drug Categories for Emergency Room Patients According to Race and Sex (Alcohol-in-Combination Excluded) DAWN 1988

White Male (N Episodes = 32,723)		Black Male (N Episodes = 39,290)	
Cocaine	34.1%	Cocaine	59.6%
Heroin	12.9	Heroin	17.7
Marijuana/Hash	9.5	PCP	9.0
Diazepam	5.9	Marijuana/Hash	8.5
Methamphetamine	4.4	Acetaminophen	1.1
White Female (N Episodes = 32,274)		**Black Female (N Episodes = 23,255)**	
Cocaine	16.6%	Cocaine	50.0%
Acetaminophen	7.7	Heroin	12.0
Aspirin	7.0	Marijuana	5.7
Diazepam	6.9	PCP	5.3
Heroin	6.8	Acetaminophen	4.2

Source: National Institute on Drug Abuse, DAWN (1988): Based on 27 metropolitan areas and a panel of emergency rooms outside these metropolitan areas; generalizations to total population cannot be made.

Patients aged 20-29 constituted 38 percent of the DAWN emergency room episodes while those aged 30-39 years accounted for 32 percent. Nine percent of the DAWN emergency room episodes were for persons 6-17 years of age. For these emergency room patients aged 10-17, 62 percent were reported as suicide attempts.

Another interesting demographic difference was in the motives for drug use involved in these emergency room episodes. The motive was reported as dependence for 56 percent of blacks compared to 41 percent of Hispanics and 29 percent of whites. Heroin accounted for 16 percent of black emergency room episodes, 18 percent of Hispanic episodes, and 10 percent of white episodes. Cocaine was reported in 56 percent of black episodes, 32 percent of Hispanic episodes, and 25 percent of white episodes. PCP was involved in 8 percent of black episodes, 6 percent of Hispanic episodes, and 3 percent of white episodes. Methamphetamine, by contrast, was more often involved in white episodes—4 percent of white episodes, compared with less than 1 percent of black episodes, and 1 percent of Hispanic episodes.

Drug Abusers in Treatment

Drug abuse treatment units tallied in the National Drug and Alcoholism Treatment Unit Survey (NDATUS) reported that 263,510 drug abusing clients were in treatment on October 30, 1987. New York State (with a total population of 17,825,000) had the largest number of clients, with 69,636, and California (total population of 27,663,000) was second, with 40,522. These two States, which include about 19 percent of the U.S. population, accounted for 42 percent of the Nation's clients. An estimated 67 percent of drug abuse clients were male, and the majority (56 percent) of clients were between the ages of 25 and 44. Youth under age 18 accounted for 15 percent of clients. Blacks and Hispanics comprised a larger proportion of the treatment population than of the general population or even of the drug-using population identified by the National Household Survey. Twenty-five percent of clients were black and 16 percent were Hispanic. Application of U.S. population estimates to NDATUS client counts resulted in rates per hundred thousand population of 203 for blacks, 200 for Hispanics, and

68 for whites (NIDA 1989d). An estimated 42 percent of drug abuse clients were intravenous drug users. Data from the State Alcohol and Drug Abuse Profile (SADAP) show that the primary drugs of abuse among treatment clients are heroin, cocaine, and marijuana. Estimates of admissions to treatment for cocaine abuse more than tripled from 1985 to 1988 (from 39,696 to 134,734) in State-supported treatment programs.

SPECIAL ISSUES RELATED TO DRUG ABUSE EPIDEMIOLOGY

Drug abuse affects Americans in many direct and indirect ways. Health consequences, drug-related crime, drug use by pregnant women, and the reduced productivity of drug abusing employees are issues that are discussed below, along with an additional discussion on the dynamic and sometimes localized nature of drug abuse patterns.

Drugs and Crime

The role of drug use in criminal activities has been a topic of continuing concern. In recent years, policymakers, health care providers, and law enforcement officials have agreed that drug use and its related criminal activities are among the most serious social problems we face.

The magnitude of this problem has been explored in detail by research projects funded by the National Institute on Drug Abuse and other institutions. Drug-related crime cost American society about $20 billion dollars in 1983 (including incarceration, adjudication, lost productivity, stolen property, etc.) (National Institute of Justice 1988). The criminal activities of each daily heroin user cost society approximately $55,000 per year (Johnson et al. 1985). The typical narcotic addict commits an average of 178 criminal offenses per year. If this result is extrapolated to an estimated 450,000 active heroin addicts living in the United States, narcotic addicts commit over 80 million crimes each year (Nurco et al. 1985). Approximately 38 percent of these crimes are drug-related, and 22 percent include other so-called "victimless crimes" such as prostitution, procuring, gambling, and alcohol violations. The remaining 40 percent include robbery and assaults, vehicle theft, shoplifting, selling stolen goods, forgery, counterfeiting, burglary and pickpocketing. Interviews conducted with juvenile delinquents in Miami, Florida, indicate that youths involved in the use and sale of crack cocaine committed an average of 880 criminal offenses per year (Inciardi 1988). Sixty-eight percent of these crimes were related to drug dealing/possession offenses, 39 percent to petty property offenses, 16 percent to major felonies, and 5 percent to vice offenses and prostitution.

Results from urinalyses done on males and females arrested for serious crimes in 14 major urban areas show that from September to December 1988, approximately 75 percent tested positive for drug use (Wish et al. 1989).

Preliminary findings from interviews conducted on 285 drug users (152 males and 133 females) living in New York City suggest that violence related to illicit drug use results more from involvement in the drug distribution network than from drug-induced violence. Other results from this project indicate that female drug users were more likely to perpetrate acts of violence against their children than male drug users (Goldstein 1988).

In summary, results from research studies indicate that narcotic addicts commit a disproportionate number of crimes, almost equally divided between 1) drug dealing/possession crimes and "victimless" offenses; and 2) personal and property offenses. Data also suggest that use of other illicit drugs is associated with an array of criminal offenses.

Drug Use During Pregnancy and Consequences

Data from the 1988 National Household Survey on Drug Abuse indicate that over 5 million women in the

child-bearing age group (age 15-44) are current users of an illicit drug, including about 1 million cocaine users and 4 million marijuana users. However, there are no data available from any national surveys or studies concerning the extent of illicit drug abuse among pregnant women. Only recently, Chasnoff (1989), reported results of a pilot study of 36 mainly urban hospitals in the U.S. with an annual delivery rate of about 155,000 infants. Illicit drug use during pregnancy varied with geographic location between 0.4 and 27 percent of mothers. Use of cocaine alone ranged from 0.2 percent to 17 percent, depending upon the location of the hospital. Chasnoff estimated that as many as 375,000 infants per year born in the U.S. may be affected by their exposure to drugs in-utero. However, an accurate national estimate of the extent of illicit drug use during pregnancy remains to be determined.

Cocaine use during pregnancy has been found to be associated with such obstetric and neonatal adverse consequences as preterm delivery, abruptio placentae, low birth weight, infants of small size for gestational age, and sudden infant death syndrome (Chasnoff et al. 1987). In addition, isolated cases of seizures, cerebral infarction, and urogenital birth defects in infants born to cocaine-abusing women have been reported.

Drug Use by Employed Persons

Drug use is most prevalent in adults aged 18 through 34 years. This age group is a major segment of our workforce. Although drug use prevalence is higher among the unemployed than among those employed, nearly 17 percent of full-time employed 18- to 25-year-olds had used marijuana in the past month. For the age group of 26 to 34 years, 11 percent of the full-time employed had used marijuana in the past month, as shown in table 8. Drug use prevalence decreased with increasing age among full-time employed people.

Drug use, including alcohol, can interfere with an employee's productivity and safe performance of job responsibilities. The use of drugs can also reduce an employee's dependability by increasing the number of days lost from work. Drug use by the members of the American workforce also carries with it the risks and problems associated with drug dependence more generally. Studies on the human and economic cost of drug abuse indicate that the direct and indirect costs of drug abuse to business are substantial. These include decreased productivity, absenteeism, accidents in the workplace, increased health care costs, the loss of trained personnel, employee theft, and the costs of prevention, treatment, and deterrence programs.

The use of drugs in certain industries, such as transportation, increases the likelihood of injuries to others. Commercial vehicle operators such as truck drivers, airline pilots, bus drivers, and train operators have responsibilities that involve the safety of others. Truck drivers are particularly at risk for using illicit drugs because almost all of them are paid by the mile or by the load. This creates an economic incentive to fight fatigue, loneliness, or boredom and keep on driving. A 1988 Regular Common Carrier Conference (RCCC) Safety Survey found that the majority of truck drivers feel that at least 20 percent of their fellow drivers regularly drive under the influence of illegal drugs (Beilock 1989). When asked to name "the two most common illegal drugs used" by their fellow truckers, the most frequently mentioned drugs were marijuana, "speed," and cocaine. The Fatal Accident Reporting System showed that about 4,500 people died in crashes involving tractor-trailer trucks in 1985 (National Highway Traffic Safety Administration 1985). The truck drivers themselves accounted for only 17 percent of those killed. Truck drivers are only one example of a high-risk occupational group. There are many other industries and job characteristics that increase an employee's potential to use illegal drugs.

TABLE 8. Percentage of Current Drug Users by Selected Drug Type, Employment Status, and Age: 1985 and 1988

Employment Status	Past Month Use Any Illicit[1]		Past Month Use Cocaine		Past Month Use Marijuana	
	1985	1988	1985	1988	1985	1988
	Percent of Population Full-Time Employed					
Both Sexes						
18–25 years	26.9	18.7	7.6	5.0	23.5	16.9
26–34 years	22.0	13.0	6.8	2.5	17.7	11.2
35+ years	6.2	2.4	1.0	0.4	3.7	1.3
All ages	15.0	8.2	4.0	1.8	11.7	6.8
	Part-Time Employed					
Both Sexes						
18–25 years	18.9	16.7	3.9	3.6	15.2	14.2
26–34 years	22.2	13.0	6.9	*	19.5	9.8
35+ years	2.9	3.6	*	*	2.4	2.7
All ages	12.6	9.4	2.2	1.9	10.2	7.5
	Unemployed					
Both Sexes						
18–25 years	38.6	28.2	13.6	6.8	33.2	25.5
26–34 years	28.2	24.8	3.1	7.9	27.3	19.6
35+ years	6.0	4.8	0.7	*	4.8	*
All ages	24.1	18.2	6.0	4.6	21.5	14.8

[1]Includes use of marijuana, hashish, inhalants, hallucinogens, cocaine, heroin, and nonmedical use of stimulants, sedatives, tranquilizers, or analgesics.

* Low precision; no estimate reported; estimates usually very small.

Source: National Household Survey on Drug Abuse, 1985 and 1988

The Dynamic Nature of Drug Abuse

The etiology of drug abuse is complex, varying over time, across geographic region, by drug, and by demographic characteristics of drug users. Peer pressure, curiosity, depression, hedonism, attempts to increase or improve performance, rebellion, alienation, and a host of other reasons have been proposed to explain why people use and abuse intoxicating substances. Etiologic studies of drug abuse serve to identify risk factors and individuals who are at risk for using drugs, adverse consequences from drugs, and possible intervention strategies and public health measures that may support prevention and risk reduc-

tion efforts. Drug abuse outbreaks tend to be geographically localized, to emerge sporadically, to be related to unique drug forms and drug analogs, and to involve specific subpopulations, all of which complicate surveillance efforts that depend on national data collection systems.

Data from DAWN have demonstrated that drug abuse patterns differ between cites. For example, methamphetamine (speed), which was mentioned in less than 2 percent of all DAWN emergency room cases and 2.4 percent of all DAWN medical examiner cases, was mentioned in 27 percent of emergency room cases and 22 percent of medical examiner cases in San Diego in 1988. PCP was mentioned in 5 percent of DAWN emergency room episodes and 18 percent of drug-related deaths nationally, but 29 percent of DAWN emergency room episodes and 18 percent of drug-related deaths in Washington, DC, were PCP-related.

In 1989, a team of medical epidemiologists from NIDA investigated an outbreak from a smokable form of methamphetamine ("ice" or "crystal") in Hawaii. This investigation was initiated to assist public health and law enforcement officials and health care providers in response to dramatic increases in methamphetamine-related treatment admissions, emergency room cases, and medical examiner reports. The study identified demographic characteristics and risk factors among the user population, and resulted in the targeting of public health intervention efforts, specifically in prevention and treatment.

Other examples of drug-related field investigations conducted by NIDA, frequently in concert with State epidemiologists, include a study of Dilaudid-related overdose deaths in the District of Columbia in 1987, a study of health consequences associated with a specific "brand name" of cocaine in Philadelphia in 1988, an investigation of overdose deaths from 3-methylfentanyl in Pittsburgh in 1988, and an investigation of use of LSD-laced transfer paper, known as "blue star."

Other field investigations are under way. One is aimed at determining the nature and extent of lead and heavy metal contamination among IV users of methamphetamine in Oregon, where there has been an increasing incidence of lead poisoning among methamphetamine drug abusers. The life-threatening complications that may result from use of contaminated methamphetamine have prompted public health officials in that State to release special bulletins notifying clinicians and health care providers to be alert to this clinical problem among suspected IV drug abusers who seek emergency medical care.

A second concern is the abuse of a potent form of heroin, termed "black tar" heroin, in the southwestern cities of El Paso, Albuquerque, and Phoenix. Here, too, there is an urgency to the investigation. As recently as October 1, 1989, there were 50 people who had overdosed on black tar heroin and sought emergency medical treatment in San Francisco over one 24-hour period; three people died as a result of the drug. This study is focusing on identifying risk factors for use of black tar heroin and on public health measures for intervention and risk reduction.

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[1]In order to enhance the value of the DAWN data, NIDA is in the process of developing a probability-based sample of emergency rooms to provide estimates for the Nation as a whole as well as for 21 metropolitan areas.

[2]Drug use prevalence can be stated in terms of either lifetime use (use at any point in the past), annual use (use one or more times in the previous year), or current use (defined as any use within the past month). All three measures are used in this chapter.

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PREVENTION RESEARCH

INTRODUCTION

This chapter describes the range of approaches that characterize the Nation's efforts to prevent drug-related problems. As the 1980s began, drug use by adolescents and young adults was at near epidemic levels (Johnston et al. 1986). Survey data available at that time revealed that 3 out of 5 high school seniors had experimented with an illicit substance and that 10 percent used marijuana daily. Currently, 47 percent of high school seniors report some experimental use of drugs, and 2.7 percent report daily marijuana use. Reductions in use can be attributed, at least in part, to better preventive approaches. Progress has not been universal. Many people, especially young adults, continue to consume alcohol daily or to drink five or more drinks regularly. Many continue to use tobacco despite their awareness of its associated health risks. Finally, cocaine use, and "crack" use in particular, appear to be

increasing, which affect both the user's health and the overall quality of life in areas in which cocaine use is rampant. These trends make the continued development and implementation of effective preventive interventions imperative.

EPIDEMIOLOGY, ETIOLOGY, AND PREVENTION

The sophistication of substance abuse prevention efforts continues to improve. Unimodal interventions (e.g., drug education, esteem building or peer resistance) are increasingly being replaced by multimodal approaches that involve children at risk, their families, even the entire community. The Office for Substance Abuse Prevention (OSAP) within the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), currently funds more than 120 community-based model demonstration programs for high-risk children. An integral part of many of these programs is forming cooperative networks among families, schools, and community agencies. Ongoing evaluations of such programs will provide important new information about the effectiveness of multidimensional approaches. As discussed later in this report, recently published findings suggest that comprehensive community-based preventive interventions represent an important weapon in the Nation's battle against drug abuse.

The Nation's ability to monitor the extent and nature of drug involvement among its citizens is also improving in sophistication and scope. Drug and alcohol use by young people at a critical point of transition in their lives (their last year of high school) is measured by the Monitoring the Future project at the University of Michigan Institute for Social Research (Johnston et al. 1986). Widely referred to as the "high school senior survey," this project, supported by the National Institute on Drug Abuse (NIDA), conducts a rigorously designed annual survey of the attitudes and behavior of randomly selected samples of 12th graders. Since 1976, longitudinal assessments of samples of earlier respondents have also been done. These data track current drug use rates among adolescents and young adults and permit comparisons with prevalence of use in prior years. (A more detailed description of this project is provided in the chapter on the nature and extent of drug abuse.)

In addition, needed epidemiological studies are planned to study drug use patterns in other segments of the population. Little is known, for example, about such patterns among the middle-aged and elderly. Reportedly, alcohol and cocaine use among the former, and abuse of alcohol and prescription drugs among the latter, merit additional attention. Much remains to be learned about the drug-related knowledge, attitudes, and behaviors of preadolescents. Our understanding of the factors that influence the decision to avoid or initiate drug use and of the critical developmental periods in which such decisions are made remains insufficient. Consistent with the shift toward community-focused interventions, surveys are also likely to consider the role of environmental characteristics, such as the visibility of drug use in the neighborhood, in encouraging or discouraging drug use. Epidemiological research is fundamental for the design of effective preventive interventions by providing insight into etiological factors (i.e., contributors to the occurrence of drug abuse). Epidemiologically identified factors can then be confirmed through prospective longitudinal studies. Increasingly, preventive trials research is used as another strategy to confirm etiological hypotheses and test simultaneously the effectiveness of preventive interventions.

The salient question for researchers is not how drug abuse can be prevented, but rather how, and under what conditions, drug abuse can be prevented among each of the subpopulations in our society. If, for example, it is determined that overestimation of their peers' drug use contributes to children's decision to use drugs, interventions can be designed to correct such misperceptions. By observing groups of children as they progress from being nonusers to being users, researchers can learn the age(s) at which preventive intervention is most needed. By better understanding

the role of environmental factors, we may also be able to reduce the likelihood of drug use in specific situations. Finding the "weakest links" (i.e., those that can most readily be changed) in a causal chain is a highly effective public health strategy for targeting preventive interventions.

Epidemiological information also identifies those segments of the population most at risk for substance involvement and the factors contributing to that risk. Some of this information has already been translated into preventive strategies. As additional epidemiological work is completed, significant gains are expected in the precision of risk identification and the design of interventions.

It is widely agreed that no single causal factor accounts for the initiation and maintenance of substance abuse (Jones and Battjes 1985). Rather, multiple determinants seem to combine to produce individual susceptibility (Orford 1985). Whether that susceptibility evolves into drug abuse depends on a combination of individual and environmental factors that are only partially understood (Sameroff and Fiese 1988; Lorion and Allen, in press; Lorion, in press a). Predicting the occurrence of alcohol and other drug use based on knowledge of these factors is, therefore, quite complex. Each factor appears to influence the impact of other factors. Being the child of an alcoholic parent, for example, represents one form of vulnerability, which may not lead to becoming an alcohol user in the absence of peers who encourage and model alcohol use. At the same time, a child's interest in alcohol may stimulate peers to experiment with it. In turn, their use may further increase the child's vulnerability, leading him or her ultimately to become an alcohol or other drug abuser.

A "transaction" refers to the interaction of individual and environmental characteristics. Unraveling the processes that characterize transactions such as the one presented above may provide a key to controlling heretofore intransigent behavioral processes (Lorion, in press a). Understanding such transactions also represents an opportunity and a complex challenge for prevention researchers. Individual vulnerability to drug abuse refers to the combined impact of biological, familial, and personality factors (Bry 1983).

Vulnerability to substance involvement, is not, however, synonymous with actual involvement (Lorion et al. 1989). Actual use depends on environmental factors such as levels of drug use among peers, peer attitudes toward use, access to and availability of drugs, and assumptions about how significant individuals in one's life will respond to one's use.

An individual's environment can enhance or moderate vulnerability, reducing or increasing personal risk. An individual's response to the environment can affect peer behavior, obstruct or facilitate access to substances, and serve to endorse or to modify parental attitudes. Further significant reductions in use are expected as better interventions are designed to address these transactional processes. In the following sections, specific individual and environmental risk factors are reviewed.

INDIVIDUAL RISK FACTORS

Biological Risks

Much is currently known about individual components, including biological and intrapersonal factors. There is increasing evidence, for example, of a genetic predisposition to developing drug problems (Goodwin 1985; Kumpfer, in press). As a group, children of alcoholics are likely to show signs of alcohol dependence at a younger age, escalate their use more rapidly, and experience more serious dependence than peers whose parents are not alcoholic. Studies focusing on twins and the adopted children of alcoholic parents confirm the inheritability of a predisposition to alcohol abuse (Schuckit 1985). Recent findings also suggest that children of alcoholics may also be at substantial risk for other kinds of drug abuse (Emshoff, in press). However, as discussed in

the section on familiar risks below, factors such as parenting skills and attitudes must be considered along with genetic vulnerability (Baumrind 1985).

Research has begun to focus on the children of drug-using parents. In an extensive review of the subject, Kumpfer (in press) reports that such children have a different physiological response to drugs compared to the offspring of nonusers. Kumpfer argues that the resulting metabolic vulnerability in these children enhances their susceptibility to becoming drug dependent. Although this research is preliminary, it supports the conclusion that at least one group of children, the offspring of alcohol and other drug abusers, may have an enhanced physiological risk for developing drug problems. NIDA is actively encouraging research to examine further the nature and extent of familial transmission of drug abuse vulnerability. We must also extend our understanding of drug abusers' physiological responses to drugs. The rapidity, intensity, and duration of the physical reinforcements associated with early drug use are likely to be important risk factors for subsequent abuse and dependence.

Psychological Risks

Research has also examined the relevance of personality characteristics. Significant, albeit weak, associations have been found between substance use and level of self-esteem (Hawkins et al. 1985), locus of control (i.e., the individual's perception of his or her responsibility for and ability to control events) (Hawkins et al. 1985; Jurich and Polson 1984), and feelings of depression (Kandel et al. 1986; Newcomb and Bentler 1986). Kaplan, Martin, and Robbins (1984) encourage drug prevention researchers to focus on the combined influences of negative self-esteem, peer attitudes toward and reinforcement of drug use, and consequent avoidance of failure and negative self-devaluing experiences as contributors to the initiation and development of dependence on drugs. Prospective longitudinal research is needed to clarify whether these associations represent antecedents, concomitants, or consequences of drug involvement.

The link between other psychological factors and drug abuse is clearer. For example, it is known that positive attitudes toward drug use and an interest in experimenting with drugs places children and adolescents at risk for actually initiating such use (Smith and Fogg 1978; Kandel 1978; Swisher and Hu 1983; Huba et al. 1981; Schegal et al. 1977). The decision to initiate use is also influenced by expectations about the social and physical consequences of use (Fors and Rojeck 1983; Smith 1980).

Behavioral Risks

Involvement in antisocial and delinquent activities also increases the individual's likelihood of engaging in drug use (Hawkins et al. 1987). Based on both retrospective and prospective studies, it is known that antisocial behavior during childhood (Wechsler and Thum 1973), especially by shy children (Kellam et al. 1983), predicts both early use and abuse. Early involvement in antisocial and delinquent behavior is also an important characteristic of high-risk adolescents. Finally, poor academic performance and a lack of educational commitment increase the likelihood of substance involvement (Hawkins et al. 1986; Jessor and Jessor 1977; Kumpfer 1986, in press; Smith and Fogg 1978, 1979; Kellam et al. 1983). Serious drug involvement problems rarely appear without prior signs of difficulty. Abuse tends to follow a history of negative attitudes toward self and others, early and continuing problems meeting personal and parental expectations regarding educational achievement, the gradual development of a social support system involving troubled peers, and increasing use of socially unacceptable behavior to achieve gratification and a sense of self-worth. Understanding the processes that drive such patterns and, more important, learning to alter them positively remains a challenge for prevention researchers.

Demographic Risks

Several demographic characteristics have been linked to drug use. For example, males have generally higher rates of abuse than do females (Kellam et al. 1983; Johnston et al. 1986). Members of minority groups, such as Blacks and Hispanics, are disproportionately represented among abusers of heroin and other "hard" drugs. Although adequately representative surveys of alcohol and other drug abuse in minority populations have not been done, it is known that these populations are overrepresented among intravenous drug abusers and have higher rates of illnesses and mortality related to drug abuse. The meaning of these differences is unclear, but they probably represent a combination of economic, social, psychological, and biological factors, such as high prevalence of drug abuse in prior generations, economic disadvantages experienced by many minority segments of society and their associated limited access to educational and occupational resources, and the consequences of growing up in neighborhoods with high levels of drug abuse by peers and significant adults. The contribution to drug involvement of "latch key" status, living in neighborhoods with high levels of drug availability, pressure to become involved in distribution, and associated violence are recognized as significant subjects for systematic research.

A most important predictor of risk for drug abuse is age at initial use. Earlier research has shown that use initiated before the age of 15 is a major risk factor for serious drug abuse problems (Kandel 1978, 1982; Kandel et al. 1986). Longitudinal prospective studies are needed to determine the rate at which that risk increases as onset occurs at successively younger ages.

ENVIRONMENTAL RISK FACTORS

Familial Risks

Parents contribute in other than genetic ways to their children's likelihood of becoming drug abusers. Children's awareness that their parents abuse drugs and are personally accepting of such behavior increases the children's risk of initiating use (Baumrind 1985; Kandel 1982). Lack of maternal involvement (Kandel 1980), lack of warmth and closeness (Kandel et al. 1986; Needle 1986; Jessor and Jessor 1977) and inconsistent parental discipline (Kandel et al. 1986) have all been linked to adolescent substance use. The exact impact of parental use and inadequate parenting skills on a child's risk is presently unknown. However, children reared by parents who use drugs and lack parenting skills are at substantial risk for developing drug problems.

That risk may be still further increased if older siblings living in the child's home are also users. Clayton and Lacey (1982) suggest that this increased risk results from the other siblings serving both as models of use and as sources of drugs. A finding that needs further examination is a report (Needle 1986) that the mere presence of older siblings in the home, independent of their involvement with drugs, increases a child's risk of experimenting with drugs. The mechanisms through which siblings influence each other are not well understood and need further study.

Social Risks

Relationships among peers have received considerable attention from prevention researchers. This emphasis reflects the link repeatedly observed between associating with peers who use drugs and an increased personal risk of using drugs (Jessor et al. 1980; Kandel 1982). Both peers' drug use and favorable attitudes toward use increase a child's risk of becoming drug involved. Moreover, perceived levels of peer use (Jessor and Jessor 1977; Kandel

1978), including overestimation of peer involvement (Whaley 1986), are also associated with increased adolescent risk.

As with familial risks, the mechanisms by which peers contribute to each other's substance involvement are still unclear. Perhaps having drug-using friends increases one's access to these substances (Miller and Crission 1980) or increases the probability of seeing others use them (Kandel 1978). Having friends who are using drugs without apparent negative consequences may also undermine an initial commitment to abstinence, and lessen the impact of messages from parents, teachers, and the media to abstain. Whatever the mechanisms, actual and perceived peer involvement is an important contributor to drug problems.

PREVENTIVE INTERVENTIONS

Outcomes and Options

As noted, a complex array of factors are involved in the etiology of drug abuse. This need not lead to the assumption that preventive efforts are doomed to failure. It should, however, lead designers of prevention programs to develop realistic timetables for achieving their objectives.

As documented below, reductions in the prevalence of drug involvement have already been made and will continue to be made. It is important, however, to recognize that as the number of drug abusers decreases, the complexity of the remaining problems may increase. Thus, in some respects, the challenge may heighten with success. This possibility exists because effective primary prevention programs reduce the number of new cases of drug abuse. As a result, prevalence estimates increasingly reflect longer-term users with significant levels of dependence and addiction. The characteristics of users who remain dependent are likely to be quite different from those of individuals who have responded to existing preventive interventions. Presumably, those with continuing problems, refractory to the available interventions, will require previously untried preventive strategies.

Thus, in assessing progress in the development of preventive interventions, program success must be interpreted in terms of prevailing epidemiological and etiological definitions of the problem. As the user population changes, the pace of reductions in use may also change. It must also be recognized that the definition of the solution can also change. During the past decade, the relative merits (and achievability) of the goals of abstinence (e.g., Durrell and Bukoski 1982; McAlister et al. 1980) or of "responsible use" (e.g., Baumrind 1985; Robins and Pryzbeck 1985) have been actively debated.

Reflecting this diversity of opinions regarding the desired outcomes for substance prevention efforts, Hawkins and colleagues (1985) have identified five specific preventive intervention objectives: total abstinence; the avoidance of regular use (discontinuation of use if experimental use has occurred); the avoidance of abuse (use that results in negative physical, psychological, or legal consequences); interruption of "gateway use" (use of tobacco, alcohol, or marijuana as precursors to use of cocaine, PCP, and other substances); and delaying the age of onset of use (not initiating use of some, or of any, substances until, for example, mid- or late adolescence).

These outcomes reflect the range of past drug abuse prevention goals. There is still considerable disagreement about the criteria for selecting among them. Some may argue, for example, that avoidance of use is the only acceptable objective. Such a position, however, ignores Johnston's data on "noncontinuation rates"—the percentage of prior users who have not used during the past year (Johnston et al. 1986). Responses to the High School Senior survey reveals that a significant number of experimental users stop using on their own. This pattern is not a rare outcome of adolescent experimentation with tobacco, alcohol, and drugs (Newcomb and Bentler 1989). Why this occurs and what, if any, long-term negative

consequences arise from limited drug abuse is unknown.

Demographic Trends in National Institute on Drug Abuse Prevention Efforts

Marked changes have occurred in prevention research efforts over the past decade. Table 1 summarizes some shifts in the demographic characteristics of participants in NIDA-supported prevention research. In 1978, only 2 percent of the programs reviewed in a comprehensive survey of substance abuse prevention programs (Schaps et al. 1981) were designed for members of ethnic minority groups. By contrast, nearly one in five projects currently funded by NIDA directs half or more of its efforts toward ethnic minorities. A decade ago, prevention activities were primarily directed toward adolescents (76 percent) and young adults (25 percent). NIDA's efforts are now designed to assist children between the ages of 6 and 12 (26 percent), adolescents (58 percent), young adults (24 percent), and older adults (18 percent). In the interim, both younger children and older adults have been added as appropriate targets for substance abuse prevention.

Additional epidemiological information is needed to determine whether the current allocation of effort across ethnic groups and age groups is an appropriate response to the demographic realities of substance abuse. Whether including preschoolers and periods of adulthood results in more effective preventive interventions has yet to be determined. If events reported in the headlines of major urban areas are an accurate reflection of the extent of drug abuse in the inner city, additional prevention efforts must be focused on minority and low-income groups.

Table 1. Comparison of Pre-1978 and Current NIDA-Supported Substance Abuse Prevention Programs*

	Programs Prior to 1987	Current NIDA Programs
Minority Group Representation in Target Populations	2%	18%
Age of Target Populations		
6—12	38%	26%
13—18	76%	58%
19—30	19%	24%
31 and older	6%	18%
Primary Focus of Programs (e.g., service delivery agents)		
Teachers	48%	28%
Family	1%	44%
Community (e.g., media)	9%	18%
Other (not specified, program staff, or risk factor research)	37%	32%

*The sum of reported percents exceeds 100 because of projects that focus on multiple groups and/or interventions.

STRATEGIES FOR INTERVENTION

Scores of strategies for preventing alcohol and drug abuse have been proposed. These strategies have differed in terms of the procedures used, the populations served (e.g., the individual drug user vs. the family vs. the peer group) and the substances targeted (e.g., single substances such as tobacco or alcohol vs. "substance use" generally). They have evolved from different etiological assumptions about drug abuse and different theories of behavioral change. This diversity underlines the limits of simply asking whether drug prevention "works" when both the definition of "works" (i.e., selection of the outcome defining success) and of "drug prevention" vary widely. Consequently, the salient question for the coming decade becomes which intervention, with which population influences the decision to use or continue to use which substance (Hawkins et al. 1987)?

Responding to that question requires a means for organizing the aforementioned diversity. Several systems for categorizing strategies have been offered. Tobler (1986), for example, organizes prevention programs in terms of intervention modality. This approach yields five categories: 1) programs providing drug information; 2) programs altering the affective (i.e., emotional) psychological status of the potential user; 3) programs modifying the potential user's relationship with and susceptibility to peers; 4) programs combining elements of 1 and 2; and 5) programs offering potential users alternatives to drug use.

Preventive interventions can also be organized in terms of the level at which the mechanism of change is to occur (Klitzner 1987). Within such a framework, interventions can be distinguished which focus on: 1) the individual (e.g., programs to increase an individual's knowledge about drugs, capacity to resist peer pressures to use drugs, or adherence to social norms); 2) the family (e.g., programs to improve family functioning or parenting skills); 3) the peer group (e.g., programs to alter peer norms or to enhance peer resistance skills); 4) the school (e.g., programs to increase the detection of violations and clarify policies regarding enforcement of drug-related offenses); 5) the community (e.g., programs to incorporate multiple interventions from other levels within an organized community-wide drug prevention effort); and 6) the larger social environment (e.g., public service announcement campaigns to encourage potential or actual users to "Just Say No!").

Finally, drug prevention programs can be differentiated in terms of their assumptions as follows: 1) substance abuse reflects inadequate or inaccurate knowledge of its physiological, psychological, and social effects; 2) substance abuse can only be avoided if the requisite knowledge and attitudes are first altered; 3) substance abuse represents an individual's attempt to overcome personal and interpersonal deficits (e.g., low self-esteem, inadequate decision making, limited interpersonal skills, and an inability to recognize and express feelings); 4) substance abuse results from encouragement to use by peers, family members, and the media. Such encouragement can be direct or indirect (e.g., modeling use or implying that limited experimentation is acceptable); and 5) substance abuse is a consequence of limited recreational alternatives. Additional assumptions can be identified with intervention implications. The physiological consequences of substance use, for example, suggest that principles of reinforcement can be used to design preventive and treatment interventions. The assumption that the mechanisms which underlie infrequent, "social" use are different from those that underlie addictive or dependent use suggests the need to design distinct preventive approaches for each of these outcomes.

Additional approaches are not now, however, the field's critical need. The challenge to prevent substance abuse has surely stimulated creativity and diversity in the design of potential solutions. The selection of programs for continuing development, dissemination, and funding now depends on evidence of effectiveness. In an early examination of prevention programs, Schaps et al. (1981) reported that no single intervention consistently prevented substance abuse.

Recent reviews support this conclusion (Hawkins et al. 1985, 1987; Klitzner 1987; Mauss et al. 1988; Moskowitz 1989; Tobler 1986). Appreciation of the complexity of mechanisms underlying substance abuse has led to the design of multidimensional approaches with evident potential for achieving desired outcomes (e.g., Pentz et al. 1989).

Whether these new approaches fulfill their promise depends on the consistency with which they can be implemented, the patience and precision with which they will be evaluated, and the support of policymakers. A decade or more may be required before the outcomes of such programs will be certain. These outcomes must be evaluated using precise, field-based methodologies which are systematically applied.

Evaluations of Preventive Interventions

The categorical frameworks described above overlap extensively. Generally, few of the categories have been systematically evaluated with scientifically acceptable methodologies. Most programs have been applied for limited time periods, with relatively homogeneous samples of white, middle-class children. Most have given insufficient attention to the fidelity of program adoption and the training of service providers. Not surprisingly, much remains to be learned about their preventive consequences. In general, a pool of mostly untested intervention strategies are now available, representing an array of opportunities for reducing drug abuse. Several general conclusions can, however, be made about their respective potential.

Consensus is developing, for example, that individual approaches which rely on a single modality have, at best, limited impact on reducing drug use (Hawkins et al. 1987; Klitzner 1987; Moskowitz 1989; Tobler 1986). Programs to increase knowledge have not done so consistently; moreover, observed changes in knowledge have rarely been accompanied by changes in attitude and drug-using behavior (Moskowitz 1989; Tobler 1986). Programs to alter individual self-esteem, to clarify "values," and to enhance individual emotional status have demonstrated little direct effect on drug use even when combined with knowledge development efforts (Tobler 1986; Klitzner 1987).

Tobler (1986) reports that interventions designed to influence an individual's relationship with peers are significantly more effective in altering substance use patterns than all other categories of interventions, singly or in combination. This effect applies to the use of tobacco as well as to alcohol, marijuana, and other drugs. One such approach is reflected in the "Life Skills Training" program developed by Botvin (Botvin and Tortu 1988). This program, for children in grades 7 through 12, uses a structured curriculum and practical exercises to improve children's skills in decision making. Participants learn the effects of substance abuse and develop cognitive-behavioral strategies for coping with anxiety, communicating with peers and adults, enhancing one's self-image and resisting peer pressure to use drugs.

This project originally reported some evidence of success. Participants were significantly less likely to initiate smoking during a 3- to 12-month period following project participation. Subsequent data suggested that reductions in alcohol and marijuana use also occurred (Botvin and Tortu 1988; Hawkins et al. 1987). The approach has been applied in both schools and a community-based recreational facility (Dusenburg et al. in press). Recent findings, however, raise questions about the long-term stability of initial gains (Moskowitz 1989). The program appears to delay, but not consistently avoid the onset of use.

A similar result has been observed with other peer-focused programs (e.g., Project SMART by Hansen et al. 1988). Rather than reflecting program failure, however, this pattern may document the limits of altering a complex behavior by intervening in a single setting over a limited time period (Mauss et al. 1988; Moskowitz 1989; Pentz et al. 1989; Tobler 1986). A child experiences multiple developmental transitions as he or she goes through school. It should not be surprising that repeated intervention contact at

successive developmental stages (Lorion in press b) may be necessary for maintaining preventive gains. Nor should it be expected that avoiding use of one substance inevitably protects one against all others. Expanding the scope and duration of available peer-intervention strategies and overcoming existing limitations of promising interventions seem reasonable immediate goals for prevention researchers.

Support for this conclusion is found in evidence of the efficacy of multimodal preventive interventions. Perry (1986) and others (Johnson and Solis 1983; Lorion 1988; Tobler 1986; Pentz et al. 1989) have argued for the advantage of comprehensive rather than site-specific interventions. Unlike school-based programs, for example, comprehensive programs reflect the fact that youth spend only a portion of their time at school. Those most involved with alcohol and drugs are also most likely to be periodically truant or no longer enrolled. Since youth spend considerable time in such settings as home, the neighborhood, and the community, NIDA's emphasis on multidimensional interventions has increased substantially over the past decade. As reported in table 1, currently, fewer than 30 percent of NIDA programs are exclusively school-based; nearly half involve the family; and support of community-based interventions has doubled to nearly one out of five. NIDA's sister organization, the Office for Substance Abuse Prevention (OSAP), has funded an increasing number of community-based prevention and intervention programs for high-risk youth and families since 1987. Increasingly, programs simultaneously involve multiple settings thus providing young people with more consistent messages about substance abuse in many areas of their lives.

Family-based programs, for example, have received increased attention. Several projects have integrated social learning approaches with interventions to improve management practices in families with children displaying aggressive behaviors associated with risk for drug use (e.g., Patterson 1982; Reid 1975; Hawkins et al. 1985). Illustrating this approach is a family-oriented project which focused on reducing risk factors for substance involvement. The program combined three family-oriented, school-based interventions: 1) home visits by "home-school liaisons" which were designed to improve communication between parents and teachers; 2) parent training classes to improve parents' child management skills; and 3) conflict resolution services to support and assist families of children with behavioral or academic problems. Preliminary findings indicate positive behavioral and academic changes among participating students. Evaluation of the impact of this approach on actual alcohol and drug use levels has not been completed (Hawkins et al. 1985).

The Midwestern Prevention Project illustrates a comprehensive intervention strategy which was school-based with community outreach (Pentz et al. 1989). Based on 5 years of program development and implementation, preliminary findings reveal that project participants reported using alcohol, tobacco, and marijuana at half the rate of nonparticipants. These results held up after 1 year and were independent of the method used to analyze the outcomes. Although the project's long-term effects remain to be determined and its overall findings must be replicated, available outcome data argue convincingly for the merits of broad-based interventions. Components of the Midwestern Prevention Project included a 10-session educational program on skills training to assist youth to resist drug use. Supporting this element was an organized homework segment involving parents and children in discussions and role playing to clarify family rules on drug use and family strategies for resisting drug use. Additionally, a structured media campaign describing the program and echoing its major themes occurred in each of the participating communities.

As exemplified by this project, the field is confronting the challenges of designing evaluation strategies for assessing the effectiveness of large scale community-wide interventions. Such methods may confirm anecdotal evidence of the positive influence of such efforts as "Just Say No," Mothers Against

Drunk Driving, and the National Federation of Parents for a Drug-Free Youth. Reportedly, these grassroots movements significantly increase the consistency of a community's antidrug messages. Apparently, youth respond to such messages with an increased awareness of and commitment to the view that any drug use is unacceptable. The development of groups such as Students Against Drunk Driving is an example of the potential value of movements that involve the group at risk as its own agent of change.

PROGRESS AND POLICY

Overall, changes in prevention research over the past decade reflect an increased appreciation of the fact that drug abuse refers not to a single problem, but to an array of problems. The implications of these problems for the well-being of the individual and the community differ widely, depending on physiological, moral, cultural, and legal factors. The simultaneous consideration of drug abuse along multiple dimensions increases understanding of the problem and, presumably, the complexity of the possible solutions. An increasing number of preventive intervention strategies reflect a better understanding of this underlying complexity. Over time, it is likely that current efforts will increase a community's ability to select an intervention and to apply it prescriptively to a specific problem.

Although it is not yet feasible to present a lengthy list of interventions of proven effectiveness, considerable progress is being made both in understanding the problem to be solved and in exploiting the multiple methods for its effective solution. The drug problem merits intense public scrutiny, and better solutions to it will result only from systematic increases in knowledge and tested experience. Recent findings and current efforts provide a basis for increased optimism.

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TREATMENT RESEARCH

INTRODUCTION

The goal of the National Institute on Drug Abuse's (NIDA) treatment research program is to provide a scientific basis for improving diagnostic and intervention services to those people who abuse and/or are dependent upon illicit drugs. Much of the research relevant to the treatment and prevention of drug abuse involves controlled laboratory studies that permit the precise manipulation and measurement of variables. However, the ultimate clinical relevance of this knowledge must be determined in less controlled treatment settings.

This chapter will review treatment research with an emphasis on the work of the past 3 years, including pharmacological and behavioral modalities of treating substance abuse, and the role of evaluation in assessing the efficacy of such efforts.

THE IMPACT OF ACQUIRED IMMUNODEFICIENCY SYNDROME ON DRUG ABUSE TREATMENT

Acquired immunodeficiency syndrome (AIDS) has had a dramatic impact on the goals of drug abuse treatment. To contain the spread of the AIDS virus, therapeutic attention must be focused on those who abuse drugs by injection, especially those who share needles, which carries with it the risk of human immunodeficiency virus (HIV) transmission (Hubbard et al. 1988). Effective drug abuse treatment must be made available to the maximum number of intravenous (IV) drug abusers as quickly as possible.

Intravenous (IV) drug abusers are a primary risk group for HIV infection and for later developing AIDS. The chief mechanism of infection in this group is sharing needles, syringes, and other injection equipment contaminated with the virus. The percentage of new AIDS cases related to IV drug use is increasing. Intravenous drug abuse is the primary causal factor in most heterosexual HIV transmission. Sexual contact with infected intravenous drug abusers or their sexual partners is a major risk factor for the spread of AIDS to the non-drug abusing population. The Centers for Disease Control (CDC) report that 30 percent of the 106,000 reported AIDS cases occurred in IV drug abusers, of whom 80 percent are heterosexual and the remainder are male homosexual/bisexuals. In the heterosexual IV drug user group, minorities have been hardest hit, representing 80 percent of this total, with Blacks at 38 percent and Hispanics 40 percent. Seven percent are white and the remainder are Asian, American Indian, and Alaskan natives (Centers for Disease Control 1989). In 72 percent of the cases of perinatal HIV transmission to newborns, mothers became infected through personal intravenous drug abuse or as a result of sexual contact with an intravenous drug abuser. Complicating the situation further is the increasing exchange of sex for cocaine or its smokable form, crack. Because of the disinhibiting effects of drug abuse addicts may engage in high risk sexual practices.

To prevent HIV transmission among drug abusers, research on intravenous drug abuse is now one of the highest priorities of NIDA (Schuster and Pickens 1988). The AIDS epidemic makes treatment and prevention of drug abuse, and especially intravenous abuse, critical. Drug abuse treatment can potentially prevent countless cases of AIDS, with their attendant personal tragedy and enormous health care costs. The threat of AIDS, unfortunately, will not be sufficient to stop drug abuse, just as smoking-related lung cancer and heart disease deaths have not eliminated cigarette smoking. Long-delayed and poorly understood adverse health consequences have only a limited influence on behavior. They do, however, have some impact. Fear of AIDS is motivating drug abusers to both change their behavior and seek treatment (Wiebel 1988). Treatment must be made available as needed, and that treatment must be made maximally effective.

SUMMARY OF TREATMENT METHODS

Drug abuse is a complex behavioral and physiological disorder with multiple causes and multiple treatments. An overview of the various treatment approaches is provided in table 1.

At the most general level, these treatments can be divided into two categories: pharmacological modalities, which affect physiological processes, and behavioral modalities, which influence behavioral or learning processes. Although this categorization is conceptually convenient, in practice both pharmacological and behavioral approaches are often combined to improve their therapeutic efficacy. Ideally, patient assessment will some day permit matching patients to specific treatment modalities based on their personal characteristics and drug abuse history. At present, a diversity of treatment modalities is believed to be desirable, because different methods may be more acceptable to, or more effective with, different patients. NIDA continues to investigate a broad range

TABLE 1: Summary of Drug Abuse Treatment Methods

Pharmacological modalities: treatment with prescribed medications.

1. **Agonist substitution:** treatment with a medication having pharmacological actions similar to the abused drug; methadone treatment of heroin addiction and nicotine chewing gum treatment of tobacco dependence are examples.

   a. **Maintenance:** chronic treatment at a stabilized dosage; methadone maintenance is an example.

   b. **Detoxification:** short-term treatment with progressively decreasing dosages to suppress withdrawal signs and symptoms following cessation of drug abuse.

2. **Antagonist treatment:** treatment with a medication that blocks the pharmacological effects of the abused drug; naltrexone treatment of heroin addiction is an example.

3. **Symptomatic treatment:** treatment with a medication whose pharmacological mechanism of action is not related to that of the abused drug, but whose effects might alter some of the symptoms of drug abuse; benzodiazepine hypnotic/tranquilizer treatment of the insomnia and anxiety associated with opioid withdrawal is an example.

Behavioral modalities: treatment with nonpharmacological methods based upon the learning of altered behavioral patterns.

1. **Verbal therapy:** a broad range of counseling and psychotherapy approaches relying primarily on talking; provided in either individual or group formats.

2. **Contingency management:** systematic scheduling of consequences to desirable or undesirable behavior so as to provide incentives for therapeutic behavior change; based on the experimentally derived operant psychology principles of Skinner.

3. **Conditioning therapy:** systematic controlled exposure to drug-related stimuli in the absence of drug abuse so as to reduce or eliminate the learned ability to elicit feelings of drug withdrawal or drug craving; based on the experimentally derived classical conditioning psychology principles of Pavlov.

4. **Therapeutic community:** relatively long-term (typically 6 months or longer) treatment in a closed residential setting emphasizing drug abstinence and the learning of new attitudes and behaviors toward drugs and toward others in society.

5. **Skill development:** a broad range of interventions intended to teach specific skills in areas where deficits are thought to contribute to drug abuse vulnerability; vocational/employment skills, job-finding skills, social skills, assertiveness skills, and relaxation/stress management skills are examples.

6. **Peer support self-help groups:** modeled after Alcoholics Anonymous, recovering abusers share their experiences and support one another in remaining drug-free; Narcotics Anonymous is an example.

of modalities, as well as the characteristics of patients responding to those treatments.

Because the development of new pharmacotherapies for treating drug abuse is unlikely to be profitable, the Federal Government has had to assume an active role in developing these drugs. NIDA now spearheads an aggressive Federal research initiative to develop improved pharmacotherapy for treating drug abuse. A 10-member Drug Development Task Force was recently formed to enlist the support of the pharmaceutical industry, administer grants to investigators, conduct a computer-assisted screening of potentially useful compounds, and oversee toxicity testing and clinical trials of the most promising drugs identified. Drugs are being sought for the following purposes: to serve as replacement therapies for abused drugs (such as methadone for heroin or nicotine gum for tobacco); blocking the effects of abused drugs; reducing craving for drugs; ameliorating drug withdrawal, and blocking toxic effects. Table 2 shows some of the drugs currently being developed.

Drug abuse is one of several activities that share the dubious distinction of being both illegal and unhealthy. From a therapeutic perspective, this dual status is both a blessing and a curse. Fear of legal consequences motivates many patients to enter treatment and encourages behavior change. But for others, fear of legal consequences leads to concealment and denial of their drug dependency until serious problems have developed. Because criminal justice factors influence drug abuse and its treatment, it is useful to study the treatment of addictive disorders that are not associated with illegal drugs. For example, studying the treatment of tobacco and alcohol addiction provides important information about the therapeutic and behavioral factors that may be common to various substance abuse disorders. This information is useful in developing more effective treatments. Study of the treatment of legal drugs also helps differentiate problems inherent in drug dependence from those related to participating in an illegal activity.

The following sections will briefly discuss research on pharmacologic, detoxification, and behavioral treatment of opioid and cocaine abuse and dependence.

TREATMENT OUTCOME EVALUATIONS

Evidence continues to accumulate indicating that drug abuse treatment is effective and that patients respond favorably to a diversity of treatment approaches. One way to assess the public health impact of drug abuse treatment is to do followup assessments of patients who have received it. These studies provide critical information about the natural history of drug abuse disorders and about the prevalence and magnitude of therapeutic changes.

Several approaches to treatment evaluation are used, including clinical trials, natural experiments, controlled observational (quasi-experimental) studies and uncontrolled observations (pre- versus post-treatment).

The controlled clinical trial offers the most rigorous approach to evaluating the success or failure of a specific treatment. In a clinical trial the patients are assigned randomly to a treatment method. Ideally no one participating in the trial or charged with rating its outcome (i.e., client, therapist, staff) should know which group is undergoing the actual test.

Natural experiments are designed with similar exacting criteria, and environmental conditions are changed affecting both groups so that outcomes can be attributed with certainty to the change in environment and not to other variations in it.

The controlled observational or quasi-experimental approach examines treatment outcomes of patients who have selected a treatment of their choice. The patient's status is evaluated at the initiation of treatment and at various points in followup, and compared with drug abusers who applied for treatment in the

TABLE 2: National Institute on Drug Abuse Drug Development Program

Opiate Treatment Agents		
Drug	Therapeutic Indication	Status
Methadone + Naloxone	Opiate maintenance therapy with lower abuse potential	Approved but not marketed
Depot Naltrexone	Long-term opiate blockade	Standard drug approved
LAAM	Opiate maintenance therapy	Phase III completed
Clonidine	Opiate detoxification	Currently in use in open trials
Buprenorphine	Opiate detoxification Opiate maintenance and blockade	Phase II
Metkephamid	Opiate maintenance therapy	Phase I
Acetorphan	Opiate maintenance therapy	Animal testing
Cocaine Treatment Agents		
Drug	Therapeutic Indication	Status
Desipramine	Treat withdrawal	Phase II
Sertraline	Treat withdrawal	Phase II
Imipramine	Treat withdrawal	Phase II
Carbamazepine	Treat withdrawal	Phase I
Mazindol	Treat withdrawal	Phase I
Flupenthixol	Treat withdrawal	Clinical evaluation
Fluoxetine	Treat cocaine and PCP withdrawal	Clinical evaluation
Nifedipine	Block euphoria	Phase II
Buprenorphine	Block euphoria	Clinical evaluation
Verapamil	Block euphoria	Animal testing
Diltiazem	Block euphoria	Animal testing
Sulpiride	Block euphoria	Animal testing
SCH23390	Block euphoria	Animal testing
L-tryptophan	Functional antagonism	Phase II
Amantadine	Maintenance therapy	Phase I
Bromocriptine	Maintenance therapy	Phase I
Methylphenidate	Maintenance therapy	Phase I
L-DOPA	Replacement therapy	Clinical evaluation
Nifedipine	Cocaine cardiotoxicity	Animal testing
Verapamil	Cocaine cardiotoxicity	Animal testing
Diltiazem	Cocaine cardiotoxicity	Animal testing
Monoclonal antibodies	PCP toxicity	Animal testing

same program who failed to initiate treatment after intake, or who dropped out of the program after a short time.

The uncontrolled observational study, the least exacting of these evaluation methods, is conducted similarly to the controlled observational method without comparing the outcome of the treated patients with any untreated similar group.

Several examples of outcome studies that have been completed are described below.

The Treatment Outcome Prospective Study (TOPS) is the largest and most comprehensive study of drug abuse treatment. It collected data on over 10,000 patients admitted for methadone maintenance, residential, or outpatient drug-free treatment to 37 drug treatment programs nationwide. These patients were then followed periodically both during and after completing treatment. A book describing the detailed findings of this comprehensive research effort has been published (Hubbard et al. 1989). The major findings of this landmark study can be simply stated: treatment works. Hubbard and his colleagues have reported rates of drug abuse during the year before treatment and either the year following treatment or, for those patients who have remained in continuous methadone maintenance, during the most recent year of treatment. Drug abuse is significantly decreased after treatment, and the amount of the decrease is greater in patients who remain in treatment longer (see figure 1).

Patients entered in residential treatments and outpatient drug-free treatment needed to remain in treatment at least 6 months before any significant impact on drug abuse was achieved. Associated problem behavior also decreased. For example, involvement in predatory crime decreased significantly as long as 3 to 5 years after treatment, as did illegal earnings (see figure 2).

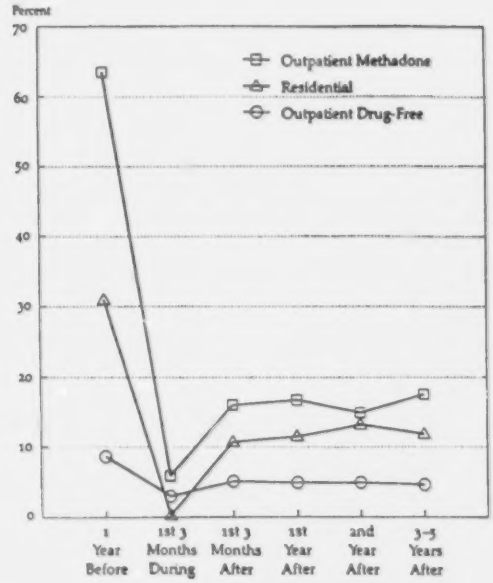

FIGURE 1. Changes in Prevalence of Regular Heroin Use Among Clients Treated 3 Months or Longer in Three Types of Programs.
SOURCE: Hubbard et al. 1989.

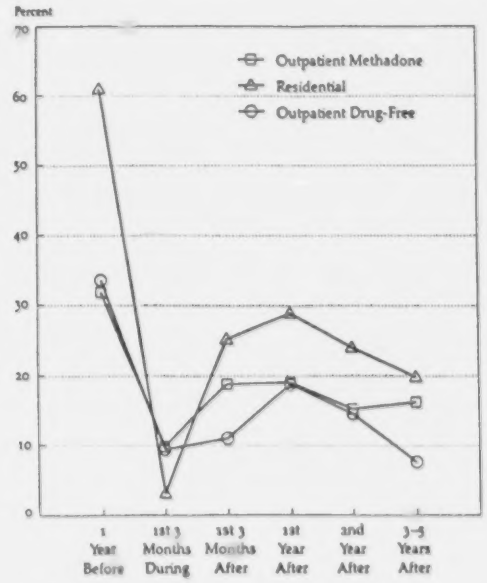

FIGURE 2. Changes in Prevalence of Predatory Crime by Clients Treated 3 Months or Longer in Three Types of Programs.
SOURCE: Hubbard et al. 1989.

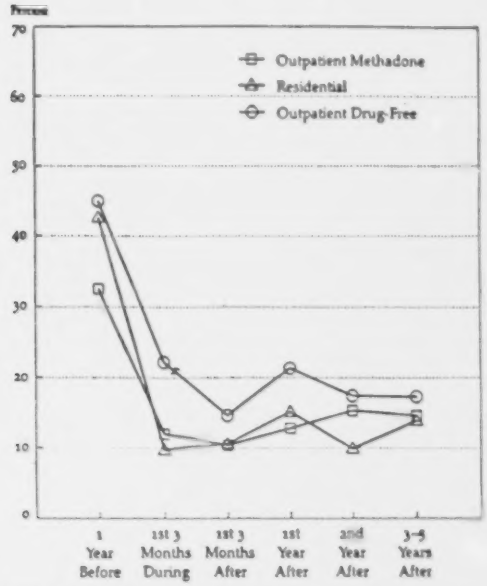

FIGURE 3. Changes in Prevalence of Suicidal Indicators Among Clients Treated 3 Months or Longer in Three Types of Programs.
SOURCE: Hubbard et al. 1989.

The frequency of suicidal thoughts and attempts also markedly decreased during, and up to 5 years after, treatment (see figure 3).

Despite these significant improvements following treatment, illicit drug abuse was still common. Moreover, none of the treatment modalities had much effect on cocaine abuse.

Simpson and colleagues (1986) have reported similar findings. Their research was based on a 12-year followup of opiate abuse patients admitted to methadone maintenance, residential, or outpatient drug-free treatment who were "tracked" by means of the Drug Abuse Reporting Program (DARP). Substantial therapeutic improvements were found at followup. For nearly two-thirds of those treated, over 3 years had elapsed since their last daily opioid abuse. The majority of these patients attributed their success to the treatment they received. These followup data emphasize, however, the chronic relapsing nature of drug abuse and the limited efficacy of any one treatment episode. Eighty-three percent of the DARP followup sample had had multiple treatment episodes, 74 percent received methadone maintenance at some time, and the median number of total treatment episodes for the sample was almost five.

Although large-scale followup studies provide valuable descriptive and correlational data concerning treatment efficacy, they cannot be used to compare the relative efficacy of different treatment modalities. In these large population studies, the decision to enter treatment and to receive a specific type of treatment is usually made by the patient. Thus, if treatment A is associated with better outcomes than treatment B, it may not mean that A is better than B. Treatment A may have been given to patients who entered treatment with a more favorable prognosis, that is, they may have been more motivated to change, had better social supports, less severe drug dependence, greater employability, fewer concurrent psychiatric problems, and so on. Controlled clinical trials in which patients are randomly assigned to the various treatments being tested are essential to document treatment efficacy more scientifically. Also, clinical trials more often employ objective evidence of drug abuse (based on urinalysis) as a critical outcome variable rather than drug use self-reports typical of large-scale treatment outcome evaluation studies.

Methadone Treatment of Opioid Abuse and Dependence

Methadone treatment continues to be one of the most widespread and cost-effective ways of treating opioid abuse and dependence. Unfortunately, its therapeutic efficacy is limited to opioid abuse; even there, it is not 100 percent effective. Clinical research on this modality continues, in an effort to understand the basis for its success and to make it still more effective.

A recent 3-year field study by the NIDA Addiction Research Center examined the outcomes of methadone maintenance treatment at 6 clinics involving 506 patients in 3 eastern U.S. cities (Ball et al. 1988). Of

the 79 percent of patients who remained in treatment for 1 year, 71 percent discontinued their IV drug abuse. Substantial reductions also occurred in patients who did not completely discontinue IV drug use. In contrast, relapse to IV drug abuse occurred within 1 year in 82 percent of treatment dropouts.

Ball's research emphasizes that methadone maintenance outcomes vary substantially among clinics. One clinic was able to report a success rate of 90 percent compared with another that reported only 45 percent. In considering these differences, the investigators stress that stability of staffing, consistent policies, and dependable treatment programs are crucial to successful therapy. They also note the importance of responding firmly and consistently to nontherapeutic patient behavior and of enforcing reasonable rules governing appropriate behavior. Similar conclusions were reached in a study at the Philadelphia Veterans' Administration Medical Center, which investigated the reasons for substantial differences in patient outcomes across different counselors (McLellan et al. 1988).

Buprenorphine Treatment of Opioid Abuse and Dependence

Over a decade ago, investigators at the NIDA Addiction Research Center conducted clinical laboratory studies of the opioid analgesic buprenorphine and concluded that it might have value in treating opioid drug abuse (Jasinski et al. 1978). Buprenorphine is an opioid mixed agonist-antagonist or partial agonist; that is, it has some methadone-like effects, but the magnitude of those effects is limited. It also has some antagonistic properties that block the effects of supplemental opioids. Discontinuation of buprenorphine after chronic dosing results in, at most, a very

TABLE 3: Comparison of Likely Different Characteristics of Opioid Abuse/Dependence Treatment With Methadone Versus Naltrexone Versus Buprenorphine

Methadone	Naltrexone	Buprenorphine
Agonist	Antagonist	Partial agonist (mixed agonist-antagonist)
Physical dependence	No physical dependence	Little or no physical dependence
Overdose possible	No overdose possible	No overdose possible
Positive subjective effects	No subjective effects	Positive subjective effects
Good patient enrollment	Poor patient enrollment	Good patient enrollment
Good patient retention	Poor patient retention	Good patient retention
Abuse potential	No abuse potential	Limited abuse potential
Produces cross-tolerance	Produces blockade	Produces blockade

mild withdrawal syndrome, although dose-dependent differences do exist in these symptoms (Kosten and Kleber 1988). In addition, methadone maintained patients appeared to have somewhat lower levels of withdrawal from buprenorphine than heroin addicts treated with the drug (Kosten and Kleber 1988). Buprenorphine appeared to have the therapeutic potential of providing, in one compound, the desirable features of both methadone and naltrexone. That is buprenorphine appears to combine the patient acceptability and cross-tolerance that make the pure agonist, methadone, clinically effective with the narcotic blockade and lack of physical dependence that make the pure antagonist, naltrexone, an attractive therapeutic compound. Table 3 provides a summary of the clinically relevant characteristics of these three pharmacological treatments for opioid abuse. This interesting new compound, buprenorphine, has now reached the stage of being clinically evaluated for its efficacy in the outpatient treatment of narcotic drug abuse.

Researchers at Johns Hopkins University Medical School have reported two clinical trials of buprenorphine in treating opioid abuse. In the first study, heroin abusers applying for outpatient treatment were randomly assigned to receive either 30 mg of oral methadone or 2 mg of buprenorphine sublingually (Bickel et al. 1988a). These daily dosages were maintained for 3 weeks, after which they were slowly reduced over the next 4 weeks to provide a gradual therapeutic detoxification. The greatest risk in treatment with a mixed agonist-antagonist such as buprenorphine is precipitating an aversive withdrawal reaction in patients. Measures of treatment success included retention, ratings of withdrawal symptoms, and urinalysis to detect illicit drug abuse, and on these measures, the buprenorphine treatment was as effective as the more routine methadone treatment. However, concurrent laboratory measures found buprenorphine was not as effective as methadone in attenuating the effects of supplemental opioid injections.

A second study was undertaken to determine whether higher doses of buprenorphine could safely be given that would produce a substantial blockade of the effects of supplemental opioid injections (Bickel et al. 1988b). Over successive 2-week periods, volunteer heroin-addict patients received various doses of sub-

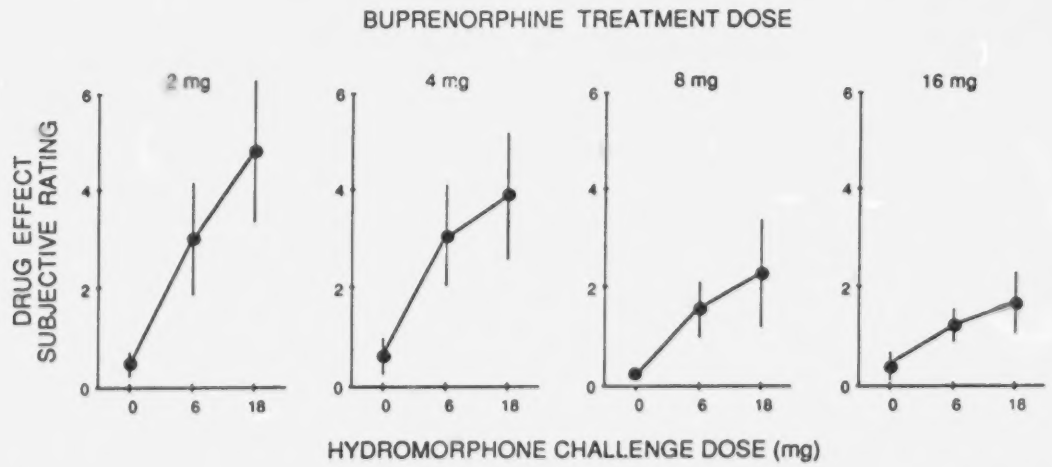

FIGURE 4: Treatment With Mixed Agonist-Antagonist Buprenorphine. This agent blocks the effects of supplementally administered opioids. Each panel shows the subjective response (feeling the opioid drug effect) following a laboratory challenge with increasing doses of hydromorphone, a heroin-like opioid agonist. The four panels show the results at four different dosages of buprenorphine treatment.

lingual buprenorphine daily. At each dosage level, a laboratory challenge test was conducted to assess the extent to which supplemental opioid effects were blocked. A sample of results is shown in figure 4. The four panels show the results of the challenge with the heroin-like agonist hydromorphone at each buprenorphine treatment dosage level. As the buprenorphine dose increased, patients became progressively less able to feel the effects of the supplemental opioid challenge dose. These higher doses of buprenorphine could be given safely without either precipitating opioid withdrawal or producing a disruptive drug intoxication. Doses between 4 and 8 mg daily were judged to produce a clinically significant degree of blockage of opioid effects, and thus were thought to constitute an appropriate therapeutic dose range.

Many patients being treated for opioid abuse in methadone maintenance programs use cocaine intravenously. A preliminary study of 138 opioid addicts treated with either methadone, naltrexone, or buprenorphine indicated that both the opioid antagonist naltrexone and the partial antagonist buprenorphine block the euphoric effects of the combination of a pure opioid agonist (methadone) with cocaine (Kosten et al. 1989). Thus these medications may be useful in treating abusers who "speedball," that is, use a combination of cocaine and a narcotic. Although a recent study has indicated that buprenorphine may have some abuse potential, it does not appear significant at this time (Hubner and Kornetsky 1988). Buprenorphine is still in an early experimental stage, and NIDA is vigorously pursuing its expedited development.

Detoxification Treatment

Two frequent and desirable goals of drug abuse treatment are to achieve and to maintain drug-free status. Achieving drug-free status is much easier than maintaining it. The treatment process for making the transition from chronic drug abuse to drug-free status is called detoxification. It usually involves the gradual reduction of dosages of the abused drug or of a drug from the same general pharmacological class which is substituted for the abused drug because it is safer. In the case of certain abused drugs, detoxification involves the abrupt termination of use followed by a period of medical supervision and treatment during the withdrawal period (a period of days to a few weeks in which the associated dysphoria and discomfort are worst). Historically, detoxification treatment has had limited long-term efficacy; most patients soon relapse to drug abuse. Because clinical and practical experience indicates that many drug abusers are ultimately able to live a drug-free life, efforts to develop improved detoxification methods continue. In addition, more successful methods might encourage increased numbers of addicts to, at least, seek detoxification, thus placing them in contact with treatment programs.

One recently developed strategy for enhancing detoxification treatment for opioid addicts uses the medication clonidine. Clonidine is marketed as a medication for controlling blood pressure, but it acts in the brain at sites that also control expression of some of the signs and symptoms of opioid withdrawal. It also has shown some efficacy in nicotine, benzodiazepine, and alcohol withdrawal (Glassman et al. 1988), though it does not prevent the seizures seen in severe cases of benzodiazepine and alcohol withdrawal. The chief advantage of clonidine in opioid detoxification is that it is not a narcotic. This fact has both legal and practical implications: physicians are more willing and able to prescribe nonnarcotics, and the lack of legal restrictions on nonnarcotics encourages their therapeutic use. At the practical level, detoxification treatment with a nonnarcotic such as clonidine can make it possible to begin treatment earlier with a narcotic antagonist such as naltrexone. Naltrexone treatment started too soon after narcotic administration may precipitate an opioid withdrawal reaction. This aversive reaction is a major obstacle to naltrexone's therapeutic use. Clonidine-assisted detoxification makes this transition from opioid abuse to opioid antagonist (naltrexone) treatment easier, more attainable, and more acceptable to patients. Clinical investigators at Yale University

have demonstrated that clonidine and naltrexone used in combination make it possible to achieve rapid opioid detoxification on a day hospital basis. Patients treated with the combination can be given a full maintenance dosage of naltrexone after 2 to 4 days (Kleber et al. 1987; Vining et al. 1988; Brewer et al. 1988).

Treatment of Cocaine Abuse and Dependence

The current cocaine epidemic poses a major problem for drug abuse treatment programs. Cocaine is generally recognized to be the most powerfully rewarding of all the drugs of abuse, and no treatment for cocaine abuse has been proven effective at the time of this writing. The major pharmacological treatments for drug abuse were developed specifically to combat opioid abuse, and they are ineffective in treating cocaine abusers. Even patients being successfully treated for their opioid abuse with methadone sometimes fall victim to cocaine. Major research efforts are underway to elucidate the biological and behavioral mechanisms involved in cocaine abuse and to develop and evaluate possible therapeutic agents. Much has been learned in the preclinical laboratory about the neurobiological mechanisms of cocaine's rewarding action and its stimulation of the brain's dopamine neurotransmitter system (Goeders and Smith 1983; Ritz et al. 1988).

Extensive laboratory and clinical studies are now underway to test the potential therapeutic efficacy of a broad range of pharmacological agents as shown in table 2, especially those thought to influence the neurotransmitter substrates through which cocaine acts (Kleber and Gawin 1987; Gawin and Ellinwood 1988). A recently completed double blind study (Gawin et al. 1989a) suggests that desipramine taken on an outpatient basis, may be useful in helping certain cocaine addicts achieve abstinence and maintain it, at least over the short term. Laboratory studies (Fischman, in press) also show some effect of desipramine in decreasing the positive effects of cocaine and of the craving for it.

Another drug, flupenthixol decanoate, has shown encouraging results in a small number of outpatient crack cocaine smokers for whom most treatments are unsuccessful. Patients receiving flupenthixol decanoate experienced a marked and rapid decrease in craving and a significant increase in the average time retained in treatment (Gawin et al. 1989b). The role of pharmacotherapy in retaining clients in treatment is important in cocaine abuse treatment as it creates a "window of opportunity" during which competing reinforcers in life can regain ascendancy and help maintain abstinence. In many of the crack using population these competing reinforcers are absent, and such individuals are difficult to treat and require extensive rehabilitation.

Contingency Management Treatment

Contingency management treatment involves attempts to change behavior by systematically manipulating its consequences. It establishes a system of rewards, punishments, or both, which provide an incentive for therapeutically desirable behavior. Investigators at the Johns Hopkins University Medical School have shown that drug abusers are sensitive to their behavior's consequences and that contingency management procedures can be effective in reducing drug abuse. Most of this research has been conducted in conjunction with methadone maintenance treatment, where methadone take-home privileges and methadone dose alterations provide convenient consequences that can be manipulated in contingency management treatment. These studies have shown that the efficacy of methadone treatment in reducing illicit drug abuse is enhanced by contingency management procedures; that is, the frequency of drug-positive urinalysis tests is lower during contingency management treatment (Higgins et al. 1986). Subsequent work has shown that positive incentives are as effective as negative incentives in reducing illicit drug abuse, and rewards have the advantage of retaining patients in treatment better than punishments (Iguchi et al. 1988).

Other investigators have suggested that negative incentives, such as threatened loss of health care workers' professional licenses, can also be therapeutically useful (Crowley et al. 1987). It has also been suggested that contingency management treatments may be especially adaptable to treating substance abusers involved with the criminal justice system (Stitzer and McCaul 1987).

Other Treatment Approaches

The selection of major treatment research domains discussed above is not an exhaustive list. Research is continuously conducted in all of the areas outlined in table 1. Only brief comments on some of these other approaches are possible here.

Laboratory studies have shown that, through a process of classical conditioning (a form of learning), the stimuli associated with drug abuse can elicit withdrawal symptoms, the subjective experience of drug craving, or both. Investigators at the Philadelphia Veterans' Administration Medical Center are investigating the value of counterconditioning procedures to reduce or eliminate the power of commonly encountered stimuli to trigger craving and drug seeking in drug abuse patients (Childress et al. 1988).

Therapeutic Communities (TCs) have evolved over the past 20 years to become groups that encourage and support social learning, emphasizing self-help methods to serve drug abusers of all kinds (Rosenthal 1989). A recent report measured the success of treatment of illicit drug users in two different TCs, between 6 months and 1 year after completing treatment. Results indicated that time spent in treatment was associated with fewer arrests as well as less drug use after graduation from the programs (Page and Mitchell 1988).

Attaining legitimate employment is often a goal of drug abuse treatment. Clinical researchers at the University of California developed and validated a Job Seeker's Workshop that substantially improved the job-seeking skills and subsequent employment of drug abuse patients. They also developed procedures for employing this effective intervention at other drug abuse treatment sites (Hall et al. 1988).

The next chapter in this volume discusses the common problem of patients having other psychiatric disorders concurrent with drug abuse. This is known as psychiatric comorbidity. Investigators have found that drug abuse patients who have concurrent psychiatric disorders, benefit significantly more when paraprofessional counseling is combined with professionally provided psychotherapy, than patients who receive only paraprofessional counseling (Woody et al. 1987).

CONCLUSION

Substantial advances continue to be made in understanding and treating drug abuse disorders. Both pharmacological and behavioral treatment modalities of demonstrated efficacy are now available. However, none of these is universally effective. Drug abuse remains a chronic relapsing condition usually requiring prolonged or repeated treatment. The methods described here have helped many patients and can be expected to help many more. At the same time, these and other approaches will be continually refined and improved to maximize their efficacy. The urgency of this mission is emphasized by the threat posed by the AIDS epidemic, and, at the same time, the mission is made more difficult by the shifting target of drug abuse. Most of the progress has been made in the treatment of opioid abuse and dependence. The recent widespread abuse of cocaine has stimulated extensive efforts to develop and apply analogous treatments for this type of drug abuse. The success of these efforts remains to be determined.

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DUAL DIAGNOSIS: DRUG ABUSE AND PSYCHIATRIC ILLNESS

INTRODUCTION

Though drug dependence is in itself a serious psychiatric disorder (American Psychiatric Association 1980; Spitzer et al. 1978), it frequently occurs in conjunction with, or secondary to, other psychiatric disorders such as depression (Woody and Blaine 1979; Dorus and Senay 1980; Rounsaville et al. 1982), organic impairment (Grant and Judd 1978; Grant et al. 1978), or schizophrenia (Ellinwood 1969; Snyder 1972). More recent research underscores this finding in other contexts. For example, Ross and his associates (1988) used the Diagnostic Interview Schedule (DIS) with 501 persons seeking assistance for alcohol and other drug abuse problems. They found that 78 percent of those seeking admission showed evidence of an additional psychiatric disorder at some point in their lives; two-thirds displayed evidence on the DIS of a current diagnosable psychiatric disorder (other than substance abuse, as such).

The most common lifetime disorders were antisocial personality disorder, phobias, psychosexual dysfunctions, major depression, and dysthymia (less severe depression). Clients who abused both alcohol and other drugs were the most likely to be psychiatrically impaired. Individuals with diagnosable psychiatric disorders were also more likely to have more serious drug problems.

Galanter and others (1988) note in a recent review that over one-third of admitted general psychiatry patients have been found to have problems that are significantly influenced or precipitated by their drug abuse. The researchers point out that it is often difficult to differentiate primary depressive disorders from those secondary to long-term substance abuse.

The Epidemiologic Catchment Area survey represents a multi-city study of the prevalence and incidence of psychiatric disorders in several major areas of the United States. Though not a representative sample of the country as a whole, these data do provide some indication of the extent of psychiatric problems in the general population. Among those diagnosed as alcohol abusers or alcohol dependent (13 percent of the total sample), nearly half (47 percent) were found to meet the criteria for at least one other psychiatric disorder (Helzer 1988).

Menicucci and his associates (1988) conclude that the problem of dual diagnosis has been previously underemphasized or ignored because of inadequate reporting, lack of a combined treatment approach, and limited research in this area.

Even the casual use of alcohol and street drugs may be associated with transient psychiatric problems in drug-abusing individuals, especially while they are actively using drugs or just after stopping use. Most psychiatrically impaired individuals have used drugs or alcohol at least briefly during their lives. However, the dual-diagnosed patients discussed in this chapter differ in two ways from these other individuals. First, they concurrently suffer from both a drug dependence disorder and one or more psychiatric disorders. Second, their improvement with respect to one disorder is not necessarily associated with improvement with respect to the other. Occasionally, treatment and improvement of one of the disorders are even associated with a worsening of the other diagnosed problem.

Patients with these concurrent disorders are variously referred to as "dual diagnosed substance abusers" (DDSAs) or as "psychiatrically severe substance abusers" (Laporte et al. 1981; McLellan et al. 1981, 1983a). They have also been referred to as the "substance abusing psychiatrically ill." Which adjective came first in this description (psychiatric or substance dependent) has historically depended more on the nature of the agency that identified these patients than upon the etiology of their disorders, their chronological relationship, or even their relative severity. Because this chapter focuses on individuals applying for drug dependence treatment, these patients will be referred to as DDSAs. It should be recognized at the outset that there are undoubtedly differences—largely unstudied subcategories—within the overall population seeking assistance from drug treatment programs, psychiatric or mental health facilities, and other types of medical or social agencies.

Estimates vary with respect to the size of this increasingly visible patient population, but there are several reasons why DDSAs are particularly important: (1) DDSAs are expensive patients to treat because they make disproportionate use of medical, legal, and social services, often under emergency conditions. Studies indicate that DDSAs require substantial administrative and treatment staff time, as well as more extensive social services. (2) DDSAs are frustrating to treatment staff in traditional mental health or substance abuse programs. They have extremely high rates of recidivism and seem to have more than the usual ability to disrupt medical and nonmedical staff relations; procedures that are usually effective do not work well with this group. (3) DDSAs are likely to become more prevalent. Several studies have indicated increases in this type of patient. This may be a real increase due to heavier drug use at an earlier age

(accompanied by family and socioeconomic disruption), the result of heightened awareness and better detection procedures, or both.

Perhaps because of the significant economic and health care delivery problems associated with these DDSA patients (Eaton and Kessler 1987; Kamerow et al. 1986), there has been a dramatic increase both in the clinical treatments offered for these patients and in the number and diversity of research studies involving the "dual disordered" patient. The past 5 years have witnessed the emergence of the "Dual Disorder Clinic," "Mentally Ill Chemical Abuser Program (MICA)," "Psychiatrically Ill Substance Abuse (PISA) Treatment Center," or other similar specialty unit in both the private and public hospitals of most States. From a clinical perspective, the emergence of these programs is evidence of the impact these patients have had on the substance abuse and mental health agencies and on the insurance programs that fund them. From a research perspective, the number of articles investigating diagnostic issues or comparative treatments among this patient population during the past decade, more than doubles the number of studies in this area published prior to 1980.

For this reason, it is not possible to fully explore all aspects of clinical and basic research done with psychiatrically ill substance abusers in the present chapter. Instead, this chapter will focus on two general areas that have shown important advances over the past 10 years. The first section of this chapter will review methodologies and results regarding the diagnosis of psychiatric illness among substance abusers, with particular emphasis on antisocial personality disorder. The second section of the chapter summarizes a 7-year series of studies investigating treatment strategies for psychiatrically ill substance abuse patients performed at the Center for Studies of Addiction at the University of Pennsylvania and the Philadelphia Veterans Administration Medical Center.

It is important to note that this chapter will focus on developments within the field of substance abuse designed to identify and treat those primary substance abusers having significant additional mental disorders. However, there is a parallel body of work that has developed over the past several years within the mental health field, focused on the identification and treatment of those primary mental health patients with additional substance abuse problems. This has been reviewed elsewhere and informative reviews of work over that past decade can be seen in Galanter 1988; Talbott 1984; Pepper 1985; or Ridgley 1986.

PART I-DIAGNOSTIC ISSUES IN DUAL DISORDER PATIENTS

Drug dependence frequently occurs in conjunction with, and/or secondary to other psychiatric disorders such as depression, anxiety, and personality disorders. Over the last several years, systematic research into the problems of the DDSA was facilitated by improvements in diagnostic criteria and by the development of structured diagnostic interviews (e.g., NIMH Diagnostic Interview Schedule, Robins et al. 1981; Schedule for Affective Disorders and Schizophrenia—Lifetime Version, Spitzer and Endicott 1978). A number of studies over the past decade have begun to provide indication of the relative rates of conjoint occurrence of substance use and other psychiatric disorders. For reviews, see Alterman (1984), Meyer (1985), Mirin (1984), and Pickens and Heston (1979). Several of the larger and better controlled of these recent diagnostic studies are summarized in table 1. This table displays the major diagnoses found among subjects in three substance abuse categories and contrasts these against a community sample of individuals from the Epidemiologic Catchment Area Study (ECA) (Regier et al. 1988), and a subgroup of individuals from this same study who also met DSMIII criteria for alcohol abuse or dependence (Helzer and Pryzbeck 1988).

Several caveats are important to note prior to the review of this table. First, all studies are not shown. There are at least 12 additional investigations of psychiatric diagnoses among substance abusers (particularly alcoholics) but these are not presented due to

Table 1: Diagnoses Among Substance Abuse Patients in Several Studies

Study Population and Researchers	N	Inst-Dia Population		Time	Any* Diagnoses Percent	Any Depression Disorder	Anxiety Disorder Percent	Panic Percent	Phobia Percent	Antisocial Personality Percent	Schizophrenic Disorder Percent
Opiate Abusers											
Rounsaville et al. 1982	533	SADS-RDC	Opiate Abuse Pts 403-M, 130-F	Life**	87	54	16	1	16	27	1
				Current	26	NA	1	NA	9	NA	0.2
Khantrzian and Treece 1985	133	DSMIII Int.	Opiate Abuse Pts 95-M, 38-F	Life	77	60	11	2	2	46	0
Woody et al. 1983	110	SADS-RDC	Opiate Abuse Pts 110-M, 0-F	Life							
Other Drug Abusers											
Ross et al. 1988	501	DIS-DSMIII	Drug Abuse Pts 260-M, 241-F	Life	84	34	62	NA	NA	47	8
				Current	68	27	45	NA	NA	37	4
Weiss et al. 1990	149	DSMIII Int.	Cocaine Abuse Pts 110-M, 39-F	Life	38	21	2	1	1	16	NA
Alcohol Abusers											
Hassin et al. 1988	123	SADS-RDC	Alcohol Abuse Pts 86-M, 37-F	Life	NA	67	28	NA	20	1	NA
Powell et al. 1982	565	PDI	Alcohol Abuse Pts	Life	63	42	NA	13	10	20	4
Hesselbrock et al. 1985	321	DIS-DSMIII	Alcohol Abuse Pts 231-M, 90-F	Life	77	38	NA	10	27	41	2
				Current							
Community Samples											
Reiger et al. 1988	19571	DIS-DSMIII	Community Sample	Life	32	9	15	2	13	3	1
				Current	15	6	7	1	6	1	1
Helzer et al. 1988	NA	DIS-DSMIII	Community Sample With Alcohol Abuse/Dep.	Life	NA	12***	NA	5	NA	12	NA

*Diagnoses other than substance abuse. NA=Not available.
**Life="Life time" rate of the disorders vs. "current" rate.
***Major depression.

lack of diagnostic specificity or because of small or unusual sample construction. Second, all diagnoses are not represented. Most of the studies surveyed provided information on a range of other diagnoses but these were not presented due to space considerations and for the sake of comparability across studies. Third, with the exception of the community sample studies reported by Regier et al. (1988) and by Helzer and Pryzbeck (1988), all of the subjects represented in this table were patients in substance abuse treatment centers or programs. This is very important in that it is likely that these treatment samples are important but nonrepresentative subgroups of the larger substance abusing population. For example, it is likely that in samples of untreated substance abusers, lower proportions would meet criteria for psychiatric diagnoses than are typically seen here (See Helzer et al. 1989). On the other hand, most substance abuse treatment programs exclude patients identified with serious psychiatric disorders or developmental disabilities. Some indication of this can be seen in the already large and expanding literature investigating substance abuse diagnoses among primary psychiatric patients and among homeless populations (e.g., Lehman et al. 1989; Ridgely 1987). These primarily psychiatric patient samples typically show more prevalence of schizophrenia, mania, and bipolar disorders and somewhat less antisocial personality disorder, yet they have similar levels of substance abuse as those patient samples summarized in table 1, who are primarily substance abusers.

Several aspects of the table 1 data deserve comment. First and most obvious is the significant variability across studies and across diagnostic categories. While it is true that the past decade has seen significant improvement in the reliability and validity of diagnoses through the development of standard criteria and diagnostic interviews, it is still the case that substantial measurement and criterion variability exists and this remains the focus of a number of ongoing research studies and reviews by professional standards committees. Among the major criterion-based problems that remain is the question of classification of psychiatric symptoms that occur in conjunction with or following the confirmation of the substance abuse/dependence diagnosis. At present, there remains dispute regarding whether symptoms that occur following the emergence of alcoholism or drug dependence should actually be considered in the determination of another psychiatric diagnosis. Antisocial personality disorder is a case in point. Many of the behavioral symptoms associated with the diagnosis of antisocial personality are behaviors which are associated directly with a protracted period of substance abuse. Examples of these overlapping behaviors include frequent job changes and criminal activity as well as the actual use of illicit substances. Obviously, these are all associated with a substance abuse/dependence diagnosis. Some have argued that considering them in the diagnosis of antisocial personality has resulted in an overestimate of this disorder among substance abuse patients (see Gerstley et al. 1989).

Other factors that may also be associated with differences in the proportions of psychiatric diagnoses seen among these treated samples include gender, primary drug of abuse, and socioeconomic status. There are demonstrated differences in the frequencies of diagnoses seen among males and females and among higher and lower socioeconomic strata individuals who are not drug/alcohol abusers (Regier et al. 1988) and this could have considerable influence on the results seen in the published studies. Several of the studies shown employed Veterans Administration samples which have higher proportions of males, usually in the lower socioeconomic strata. In contrast, other studies report mixed male and female subjects, some from higher socioeconomic strata. Because of the substantial variability seen with different diagnostic criteria and with different mixes of gender and socioeconomic strata it is not possible at this time to draw conclusions or even comment on the relative frequencies of different diagnoses among the various substance abuse samples; although there is some indication that drug users who prefer particular types of substances for regular use have different patterns of psychiatric diagnoses (see McLellan et al. 1980; discussed in part II).

Despite the likelihood that differences in diagnostic criteria, gender, socioeconomic status, and drug preference of the subjects explain some of the variability in the diagnostic patterns observed in the studies summarized in table 1, it is also clear that the substance abuse samples generally have higher proportions in every disorder category than community samples. For example, studies of drug and alcohol abusers in treatment have reported lifetime diagnostic rates ranging from 21 to 67 percent for the depression disorders (major, minor, intermittent, and dysthymia) as compared with a community sample rate of 9 percent in the Regier et al. (1988) study. Similarly, while there is again substantial variability across samples, the majority of reported studies indicate lifetime rates of anxiety disorders (usually generalized anxiety disorder) over 15 percent among treated substance abusers, but the community samples generally show rates lower than 15 percent. Rates of reported antisocial personality disorder among these treated samples are usually over 20 percent while the community rate is approximately 3 percent.

Thus, while there is clearly additional work needed to compare treated and untreated samples of substance abusers with appropriately matched (age, gender, socioeconomic status) samples of nonabusers, using identical criteria and interviews, it is equally clear that substance abusers in treatment programs are likely to have elevated rates of depression and anxiety disorders as well as antisocial personality disorder. Similar findings are also seen in community samples through comparison of the diagnostic rates for the overall ECA data (Regier et al. 1988) and those individuals from the ECA sample who met diagnostic criteria for at least one lifetime disorder; among those who did, 32 percent met criteria for alcohol abuse/dependence (Helzer and Pryzbeck 1988). In the Helzer study, these authors found that approximately 34 percent of subjects in the Epidemiologic Catchment Area (ECA) sample met DSMIII criteria for an additional disorder. However, among those who met diagnostic criteria for alcohol abuse/dependence (17 percent of population), 47 percent met criteria for an additional diagnosis. The distribution of these diagnoses is presented in the last line of table 1. Thus even among community samples the presence of a substance abuse diagnosis (in this case alcohol abuse/dependence) was associated with disproportionately high rates of other psychiatric disorders. In fact, in that study the correlation between the number of substance abuse diagnoses and the number of non-substance abuse psychiatric diagnoses was 0.98.

A Special Note on Antisocial Personality Disorder—As can be seen from the table 1 data, a general conclusion can be made that the frequency of psychiatric diagnoses among samples of substance abusers (whether in or out of treatment) is higher than for comparable matched samples of nonabusers; but there is less certainty regarding the "true" rates of most specific disorders among particular samples. Despite this general caution, one diagnosis that is clearly elevated among substance abuse samples over comparison samples by as much as 100 to 4,000 percent is the diagnosis of antisocial personality disorder. Again, while there is substantial variability in this diagnosis as in all others, in the proportion of those included in the category (especially among substance abusing samples) two conclusions remain. First, regardless of the criteria used, substance abusers have much higher rates of this disorder than nonabusers and this is true for both males and females in high and low socioeconomic groups. Second and most important, the available evidence suggests that the diagnosis is clearly associated with poor response to substance abuse treatment, regardless of the type of substance use or the type of substance abuse treatment. The presence of any psychiatric disorder appears to be associated with poorer treatment response in standard substance abuse treatments (Powell and Pennick 1982; Rounsaville 1987; McLellan et al. 1983). Psycho-therapies and/or pharmacotherapies in addition to standard substance abuse treatments appear to improve the rehabilitation of drug and alcohol abusers with anxiety, depression, or phobias (Woody et al. 1983, 1984; Gawin and Kleber 1986; Arndt et al. 1990). However, there is no evidence available at this time that any combination of psychotherapies, behavioral therapies, or pharmacotherapies has been effective with antiso-

cial substance abusers (Woody et al. 1985; Stabenau 1984; Powell et al. 1982).

As indicated above, there has been considerable debate over the criteria used to diagnose this disorder and this has been discussed in detail by Gerstley et al. (1989) and by Cooney et al. (1990). Gerstley and her colleagues describe how early formulations of this disorder emphasized the sociopathic qualities of this diagnostic group, focusing on lack of empathy and warmth; and the inability to develop meaningful personal relationships. More recent versions have focused on the behavioral ramifications of these "underlying" traits, targeting criminal behavior, irresponsible behavior at school and work, and the abuse of substances. These different diagnostic criteria obviously lead to different inclusion rates and there is at least some indication that these diagnostic considerations are related to treatment response. For example, Gerstley et al. (1988) found variability among DSMIII diagnosed antisocial opiate addicts with regard to the ability to form a "helping relationship" with a therapist and that those who were able to develop this relationship during treatment had somewhat better outcomes than other antisocial opiate abusers. Similarly, Woody et al. (1985) found that those antisocial opiate abusers who met diagnostic criteria for depression in addition to criteria for antisocial personality disorder had a slightly better treatment response than other antisocial substance abusers in the same program. These findings suggest that there may be some important differences among antisocial substance abusers that could lead to the development of more effective treatments and these avenues should be explored in future research. However, at this point it must be stated that the antisocial substance abuser represents a large segment of the substance abuse population and one for which treatment results have been unimpressive.

Clearly the presence of additional psychiatric diagnoses, whether axis II personality disorders or other axis I disorders, has implications for the treatment of substance abuse problems in the dual-disordered population as well as their psychiatric problems. This will be discussed in part II of the present chapter.

PART II - TREATMENT STRATEGIES FOR DUAL DISORDERED PATIENTS

In this part, the emphasis will be on illustrative experiences with DDSAs in a single setting and on attempts at describing and treating males who were primarily opiate abusers. Some of the data based on this group may not pertain directly to other classes of substance abusers or to female or adolescent substance abusers. It is hoped, however, that the methods used are pertinent to DDSAs of more varied demographic and socioeconomic subtypes. A brief summary of recent research findings on populations that have been described by others is also included.

Material dealing with this population is presented in two parts. The first part reviews early studies, which attempted to identify these patients and to describe the relationships between their drug of choice and their psychiatric symptoms. The second part reviews a series of clinical studies specifically aimed at developing appropriate and effective methods for treating these patients.

Relationships Between Drug Of Choice And Psychiatric Diagnosis

Anecdotal reports had suggested that alcohol and street drugs were being widely abused by psychiatric patients being treated at the Coatesville Veterans Administration Medical Center, a 1,400-bed psychiatric facility located near Philadelphia. To obtain more specific information on the nature and extent of this problem, confidential interviews were conducted with a randomly selected sample of 166 male psychiatric patients who had no recorded diagnosis of alcohol or other drug dependence.

All the interviews were conducted individually and with complete privacy. Patients were asked questions regarding the nature and severity of their drug use. This survey (McLellan et al. 1978) found that half the sample had serious substance dependence problems that they had not reported to the treatment staff. This confirmed the existence of a large, previously unknown group of substance-abusing psychiatric patients. The magnitude of the problem is still more apparent when this group is combined with that of psychiatric patients who have previously acknowledged abusing drugs (that is, those with a recorded substance dependence diagnosis). This "known group" has been estimated as 35 to 45 percent of most psychiatric populations (Alterman et al. 1980; Crowley et al. 1974; Hekimon and Gershon 1968).

Another aspect of this problem is the prevalence and potential importance of psychiatric problems within the primary drug dependence patient population. As a means of determining both the point prevalence and the changes in the population over time, comparisons were made of the demographic characteristics, substance use, and various psychiatric variables (McLellan et al. 1979a) of two randomly selected patient samples admitted to inpatient drug dependence treatment units during 1972 and 1978. This study found significant and pervasive differences in the admission characteristics of drug abuse patients treated in each of those years. In general, there were major increases in the number and severity of the psychiatric problems at the time of admission in the 1978 sample compared with the 1972 sample. Specifically, the 1978 group showed significantly greater pathology on the Minnesota Multiphasic Personality Inventory (MMPI), a widely used profile of psychiatrically relevant dimensions. The 1978 group had higher scores on scales of depression, psychopathic deviance, paranoia, hysteria, and schizophrenia. At that time, the increase in psychiatric symptoms was observed to be associated with a corresponding shift in the patterns of drug use—away from primary use of opiates to the regular use of amphetamines, hallucinogens, barbiturates, and benzodiazepines. These observations were, however, at best correlational and could not be directly attributed to the use of these drugs.

In a followup of these clinical observations of symptom-correlated drug use, more specific information was sought on the relationship between the type of substance used and the type of psychiatric symptomatology (McLellan and Druley 1977). To do this, analyses were made of the MMPI profiles of 158 drug abuse patients, divided into groups by their primary drug of choice.

Three groups of subjects were identified by their reported (as confirmed by urinalysis) primary drug use: 15 stimulant drug users (of amphetamines, hallucinogens, or methylphenidate); 110 depressant drug users (of heroin, methadone, and other opiates); and 33 mixed drug users with regular concurrent use (at least three times per week) of depressants and stimulants. The medical history and demographic data showed few differences among the groups, and the results of their MMPI testing are in table 1. All testing was supervised and conducted approximately 5 to 7 days after detoxification to minimize drug withdrawal effects. As can be seen, the depressant group had generally lower MMPI scores than the other two groups, indicating generally lower levels of psychopathology. This was especially true in the area of general pathology (F scale), paranoia (Pa scale), psychasthenia (Pt scale), and schizophrenia (Sc scale), which were all significantly (p) different among the groups (McLellan et al. 1979a).

The subjects in this study reported concurrent use of drugs with similar psychophysiological effects. However, in the recent wave of cocaine abuse in this country, there has been more concurrent use of substances with different pharmacological and psychotropic effects.

Patients divided into groups based upon their patterns of drug use could be reliably differentiated by their psychological symptomatology measured through MMPI testing. Specifically, subjects who reported use of multiple depressants typically showed

psychological symptoms of depression (measured by the D scale) and psychopathic deviance (measured by the Pd scale). These results, though only correlational, suggested the presence of a character or personality disorder with underlying depression (Dahlstrom and Welsh 1960; Gilberstadt and Duker 1965). Those subjects who reported use of stimulants either alone or with other agents showed very high levels of psychological symptoms generally, with specific elevations on scales related to schizophrenia, mania, and paranoia, the so-called psychotic triad of the MMPI. These elevations suggest the presence of more serious psychotic symptoms such as cognitive disturbance, suspiciousness, and marked confusion (Dahlstrom and Welsh 1960; Gilberstadt and Duker 1965).

Thus, a pattern emerged of increased psychiatric symptomatology associated with multiple drug use, especially with nonopiate drugs. This and other early studies provided useful information, but the data remained simply correlational with no indication of causality. However, the data from these early explorations identified a sample of substance abuse patients who had been initially admitted to inpatient drug abuse treatment during 1971-72 and had demonstrated a pattern of virtually continuous drug abuse since that time, punctuated only by multiple readmissions for further treatment. The readmission records of these patients provided information on their intake status, psychiatric assessments, psychological testing, and within-treatment progress over a 6-year period. This also provided an opportunity to examine the longitudinal relationship between patterns of prolonged substance abuse and the development of psychiatric disorders (McLellan et al. 1979b).

The sample used consisted of 51 male veterans admitted to inpatient drug abuse treatment at the Coatesville Veterans' Administration Medical Center during 1971-72, who had been readmitted for treatment there a minimum of six times since. This 1978 retrospective sample represented all of the patients meeting the readmission frequency criterion. These patients were divided into three groups, based on their primary drug preferences in 1971-72. The 11 patients in group 1 reported that their primary drug use was of stimulants (including hallucinogens, amphetamines, and inhalants). The 14 patients in group 2 reported primary use of depressants (including barbiturates, benzodiazepines, and sedative hypnotics). The 23 patients in group 3 reported primary use of opiates, such as heroin, methadone, and related synthetic drugs.

The major purpose of this research was to examine the change in drug problems and psychological status within these three groups over their 6-year treatment history. The initial psychiatric examinations of these individuals, as well as their postdetoxification psychological testing in 1972, found low levels of psychological symptoms and no significant differences between the groups. Reassessment after 6 years of virtually unremitting use of these drugs showed clear differences among the groups. By 1978, 5 of the 11 stimulant users had been diagnosed as paranoid schizophrenic and had required primary treatment on a locked psychiatric ward. These patients were no longer suitable for treatment in the drug abuse program; four of them remained in this psychiatric state for more than a year.

Significant psychiatric illness had also developed in the depressant users, although it was quite different from that seen in the stimulant users. Anxiety and depression spectrum disease (but no psychosis) were diagnosed in 8 of the 14 users of depressant drugs; 4 required referral and primary treatment on an inpatient psychiatric ward. Of the depressant users, 11 reported suicidal ideation, and 5 had attempted suicide by 1978. In addition, psychological test data suggested significant increases in cognitive impairment (brain damage) in this group.

In contrast to these findings, the 1978 psychiatric interviews and psychological testing of the opiate users found no significant differences from the 1972 data. No psychiatric disorders other than sociopathy were detected. These 1978 differences among the three groups were consistent and quite significant. For the first time, there was evidence of measurable per-

sonality alterations associated with and specific to the chronic use of particular street drugs (McLellan et al. 1979b).

Two explanations have been suggested for the increases in psychiatric symptoms of the stimulant and depressant groups. First, it is possible that the patients in these groups may have already developed underlying symptoms of their subsequent disorders by 1972, but these symptoms were below the threshold for detection at that time. These patients may have required, or responded preferentially to, particular drug combinations because of their underlying psychiatric symptoms. Thus, even though the drugs may not have prevented the subsequent expression of their psychiatric disorders, they may have provided some temporary relief. This self-medication hypothesis is one explanation for patient selection of chemical agents with similar psychophysiological effects.

Given this self-medication explanation, the use of benzodiazepines, alcohol, and barbiturates by patients with underlying depression is reasonable. Symptoms of anxiety, melancholy, and insomnia could be temporarily ameliorated by the anxiety-reducing (anxiolytic), mood-elevating (euphoriant), and sleep-inducing (soporific) effects of these drugs.

The use of amphetamine and amphetamine-like compounds by patients with latent psychoses is less easily understood.

A second possible explanation for the psychiatric symptom increases in the stimulant and depressant groups is that prolonged abuse of the specific combination of street drugs played a direct causal role in the resulting disorders. This developmental view suggests that, although these subjects may have had undetected symptoms in 1972 and may have eventually developed a form of psychiatric illness regardless of drug use, regular consumption of particular street drugs may have hastened this development and determined the nature of the subsequent disorder. The mechanism(s) by which the particular drug combination could determine the nature of psychiatric disorder is at this time unclear, although there is earlier evidence that regular amphetamine use can precipitate psychosis.

The absence of significant increases in psychiatric symptoms in the opiate group may be due to the specific psychopharmacological effects of the opiate drugs. For example, morphine was used as an antipsychotic drug and as an antidepressant before the development of more modern psychotropic agents. Thus, methadone, morphine, and to some extent, heroin may serve to medicate underlying psychological problems, reducing symptoms of anxiety, depression, and paranoia. It is even possible that opiates may sometimes prevent the development of major psychiatric disorders, although it must be stressed that there are no data to support this speculation.

TREATMENT IMPLICATIONS

Identifying the Dual-Diagnosis Substance Abuser

Although the exploratory findings summarized above did not permit a definitive understanding of the interactions of drug abuse and psychiatric disorders, there were clear implications that the drug abuse treatment programs, which had proven effective with the majority of the substance abusers treated (McLellan 1982), might be only marginally effective with the DDSA population. To investigate this possibility more carefully, it was necessary to identify these patients easily, reliably, and validly and to evaluate their response to the conventional treatment modalities. To this end, a structured clinical research interview was designed to assess problem severity in seven areas that are often affected by alcohol and other drug dependence: medicine, law, substance abuse, employment, family, and psychiatric functioning. This interview, the Addiction Severity Inventory Index (ASI) (McLellan et al. 1980, 1985), can be administered by an easily trained technician in approximately 45 minutes.

In each of the seven ASI areas, objective questions are asked to measure the number, frequency, and duration of symptoms both over the patients' lifetime and in the past 30 days. The patient also supplies a subjective report of the recent (within the past 30 days) severity and importance of each problem area. The interviewer assimilates the two types of information to produce seven global ratings reflecting problem severity in each area. These 10-point (0=no problem, 9=extreme problem) ratings provide reliable and valid estimates of problem severity for both alcohol- and other drug-dependent patients. The individual objective items also provide a comprehensive basis for assessment at treatment admission and at subsequent evaluation points (McLellan et al. 1985).

Description of the ASI Psychiatric Severity Scale

The 10-point ASI rating of psychiatric severity is made without regard to drug use, family, employment, or other problems, which are assessed separately. In the case of psychiatric severity, some of the more prominent items elicit the patients' experience with "significant periods" of depression, anxiety, confusion, persecution or paranoia, inability to concentrate, inability to control violent tendencies, and the like. This is a very basic, global estimate of symptom severity, psychopathology, or psychological health or sickness. It most resembles the Health-Sickness Rating Scale (Luborsky and Bachrach 1974), which has now been adopted as the Global Assessment Scale and included in the Schedule of Affective Disorders and Schizophrenia (Endicott and Spitzer 1976). Intercorrelation of these measures in several studies yields coefficients that are uniformly 0.70 or above. Previously published evidence for the high reliability of this psychiatric severity rating has now been confirmed in 3 different treatment sites using 12 raters (McLellan et al. 1985). The ASI psychiatric severity scale has been correlated with standardized psychological tests and has produced the following coefficients: Maudsley Neuroticism Scale, 0.69; Beck Depression Inventory, 0.71; total score on the Hopkins Symptom Checklist, 0.81; and a measure of cognitive impairment, 0.62 (but not IQ=0.13). Thus, there is good evidence that the ASI Psychiatric Severity Scale is a reliable and valid global estimate of the severity of psychopathology, although it does not designate the particular diagnostic type.

Defining the High-Severity Patient

The ASI psychiatric scale has been used for identifying substance-abusing patients with clear psychiatric problems. In several studies, patients have been divided into low-, mid-, and high-level groups on the basis of their psychiatric severity rating at admission. This has been done on statistical grounds with low- and high-level patients rated, respectively, as less or more than 1 standard deviation from the population mean on the 10-point ASI scale. Thus, the mid-level group usually composed 60 to 70 percent of the patient population, whereas the low- and high-level groups each made up 15 to 20 percent of the total group (Laporte et al. 1981; McLellan et al. 1981, 1983a). Patients who were rated in the low-level group were generally asymptomatic or had only slight problems of anxiety or minor depression in their past. Mid-level patients may have had recent symptoms of depression, anxiety, or cognitive confusion, but no clear history of recurring symptoms. Patients in the high-level group generally reported suicidal ideation, thought disorder, or cognitive confusion. Again, it is important to note that the designation is made on the basis of symptom severity, not diagnosis or specific symptom patterns.

Determining Appropriate Treatment for the Dual-Diagnosed Drug Abuser

An initial designation of low-, mid-, and high-severity patients was made after having conducted a 4-year treatment outcome prediction study examining 742 male alcohol- and other drug-dependent patients treated in 6 different rehabilitation programs (McLellan et al. 1983a,b). In that study, it was discovered that the ASI Psychiatric Severity Scale was the single

best predictor of treatment outcome across all programs for both alcohol- and other drug-dependent populations (McLellan et al. 1983a). When these samples were divided into diagnostic groups, it was found that low-severity patients were likely to show the maximum improvement regardless of the type of treatment they received, that mid-severity patients could be matched to the most appropriate and cost-effective treatment based upon a knowledge of several other background factors, and that the high-severity patients, both alcohol and other drug dependent, were likely to show the least improvement and the poorest outcome regardless of the type of treatment they received (McLellan et al. 1983a,b).

Given the implications of these findings, it was necessary to examine the treatment response of the three psychiatric severity groups in greater detail (Laporte et al. 1981; McLellan et al. 1981). To this end, a comparison was made of the admission and 6-month followup evaluation data from the ASI on the three psychiatric severity groups of drug-dependent patients treated in either a therapeutic community (TC) or a methadone maintenance (MM) program. These results indicated considerable improvement by all groups on measures of drug abuse. The low- and mid-severity groups also showed improvement in several other areas such as employment, criminality, and family relations. The high-level group had improved least on virtually all measures. Their overall followup status was approximately the level at which the low- and mid-severity groups had entered treatment. Obviously, these high-severity patients were in danger of recidivism and readmission after only 6 months (Laporte et al. 1981).

Choosing the Best Alternative: Therapeutic Community (TC) or Methadone Maintenance (MM)

Despite the disappointing results of treatment for the high-severity group of drug abusers, the question remained as to how to treat the 15 to 20 percent of patients who are in that group. Staff from both the MM and TC programs recognized their limitations with these patients. Treatment of these patients in the inpatient psychiatric unit was virtually prohibited by the admitting staff of those units. Given the limited alternatives available, it is important to compare the effectiveness of available programs for the high-severity patient and to examine treatment duration specifically. It seemed reasonable to assume that this type of patient might respond more slowly to treatment and therefore require more extended treatment than the conventional 90-day program provided in the TC program (McLellan et al. 1984).

Rates of improvement were compared on the ASI criteria of drug use, employment, and criminality for 118 patients admitted to the TC and 154 patients admitted to the MM program during 1980. Each of these samples was divided into low-, mid-, and high-severity groups by their admission scores on the ASI Psychiatric Severity Scale. The percent improvement scores were calculated for the three criteria by subtracting the ASI followup criterion score from its corresponding admission score and dividing the result by the admission score. The quotient was a measure of percent improvement from admission to 6-month followup on each of the three criteria.

Low-Severity Patients

Figure 1 presents the regression plots illustrating the treatment duration-percent improvement relationships on the three outcome measures for low psychiatric severity in the TC (29 patients, left panel) and the MM (38 patients, right panel) programs. These regression lines are idealized and are not exact measures of patient improvement at all points along the line.

General similarities among the functions for both programs can be seen in figure 1. For all measures in each program, there was a direct relationship between time spent in treatment and the amount of positive change. Patients who dropped out early showed less improvement (some measures showed worsening)

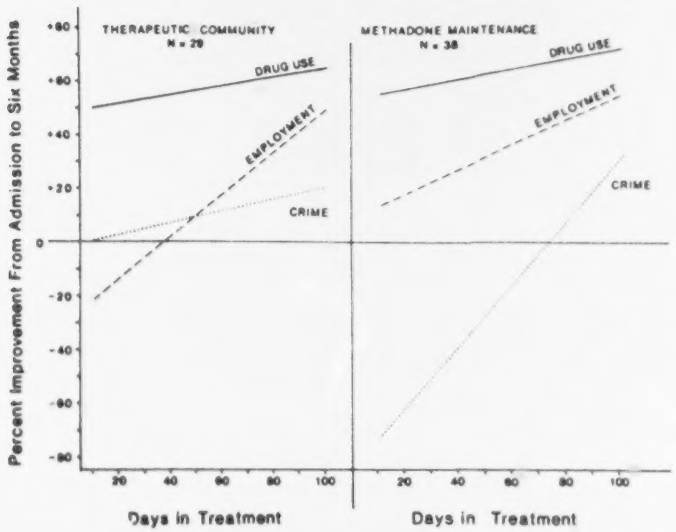

FIGURE 1. Improvement in Drug Use, Employment, and Criminality for Low-Severity Patients. Regression plots represent the best linear estimate of percent improvement per number of treatment days. The solid line in the center of the two panels indicates no change from admission to 6-month followup, while the areas above and below the line indicate improvement and worsening, respectively. The approximate midpoint of the line indicates the mean percent improvement for the groups, while the slope of the line indicates the extent to which more days of treatment were associated with greater percent improvement.

than patients who stayed in treatment longer. Clearly, there were some differences in the functions and in the absolute amounts of improvement shown. For both programs, the drug use measure showed the most immediate changes and the greatest absolute amount of improvement. Change in employment was less immediate and showed less total improvement, but equal treatment durations produced greater changes in patient improvement. This is illustrated by the steeper slope of the function and suggests that comparable amounts of treatment have quantitatively different effects on the outcome measures. The criminality measure showed significant worsening in TC patients in treatment for less than 30 days, but with more extended treatment (up to 90 days), there was significant positive change. Similar effects were seen for

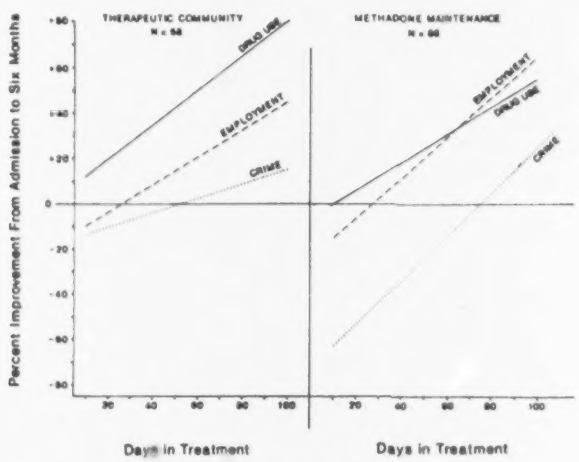

FIGURE 2. Improvement in Drug Use, Employment, and Criminality for Mid-Severity Patients.

the MM patients on the criminality measure, but beginning only after 70 days in treatment.

Mid-Severity Patients

Figure 2 presents the same relationships for 52 and 86 mid-severity patients treated in the TC and MM programs, respectively. The relationships presented are again similar between the programs and quite comparable to those seen in figure 1. The plots for these mid-level patients, however, are steeper on all measures than are those for the low-severity patients, suggesting a greater effect of treatment duration. Furthermore, similar plots for the criminality and employment measures in the TC patients and for the criminality and drug use measures in the MM patients indicate worse status at 6 months than at admission for patients who stayed in treatment only a short time.

High-Severity Patients

Figure 3 presents the same relationships for 28 and 30 high-severity patients treated in the TC and the MM programs, respectively. As can be seen, there were qualitative differences in the percent improvement functions between the treatment programs. The functions for the MM patients are similar to those shown in figure 2, with relatively flat slopes, indicative of an attenuated treatment duration effect; however, the absolute levels of improvement shown were substantially lower than those of the low- and mid-level severity groups for all treatment durations. In fact, the employment measure did not show a net improvement until after 70 days of treatment, and the criminality measure never showed a net improvement.

The percent improvement functions for the high-severity TC patients were unlike those seen in any other group for either program. For each measure, there was a negative relation between time in treatment and the percent improvement, especially in the measures of drug use and criminality. These plots indicate that high-severity patients who stayed in TC treatment for longer durations showed less improvement (in fact worsening) than those who stayed shorter amounts of time.

Two conclusions can be drawn from these results. First, treatment was effective across groups for most patients and outcome measures. The effectiveness of drug abuse treatment in an earlier sample was reported (McLellan et al. 1982), and these data continue to indicate that treatment is associated with significant positive changes. There was also a clear and direct relationship between treatment duration and amount of improvement—those patients who remained in treat-

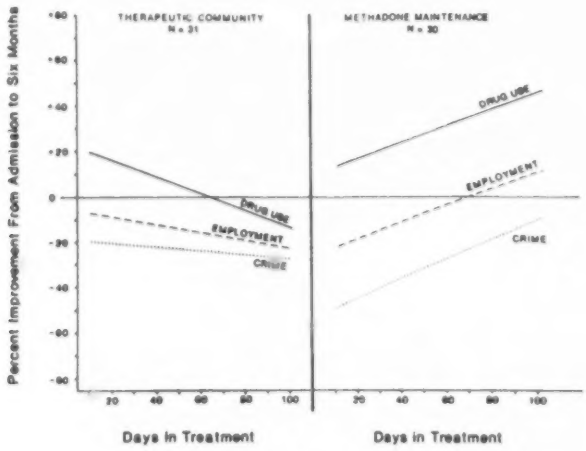

FIGURE 3. Improvement in Drug Use, Employment, and Criminality for High-Severity Patients.

ment longest showed the most improvement and the best outcomes.

The second conclusion from these results is that the severity of psychiatric status was an important predictor of treatment response generally and of differential treatment response in the more impaired drug abuse patients. Results of these and previous (Laporte et al. 1981; McLellan et al. 1981, 1983a) analyses indicate that patients with the fewest psychiatric problems at admission generally show the greatest improvement and the best outcomes. Patients with the highest levels of pretreatment psychiatric problems show the least improvement and the poorest outcomes. The additional finding from these data was that the psychiatric severity measure was also a predictor of a differential treatment response. Specifically with high-severity patients, longer treatment durations were associated with some additional improvement in the MM program, but not in the TC program. High-severity patients who stayed in the TC program for longer periods showed less improvement than similar patients who remained in the program for shorter periods of time.

It appears that the TC program was counterproductive for these high-severity patients. The explanation for this probably lies in the therapeutic techniques used in the TC modality. Most drug-free TC programs are based upon the Synanon model and were implemented in 1971 primarily for treating heroin addicts. The goals of the program are quite clear: the responsible use of alcohol and the total elimination of all other drug use, including that of marijuana. There is a general sanction against the use of psychotropic medications during treatment, although some antidepressant medications have been prescribed. Therapy is conducted by paraprofessional and ex-addict counselors, three to five times per week, usually through group encounter. The primary agent of therapeutic change is the community itself. The therapeutic community sets rigorous behavioral guidelines and polices its members strictly, meting out punishments to offenders that usually include public admission of guilt, followed by an embarrassing penance.

Evaluations of the TC modality indicate that these techniques are generally quite effective, especially for the more intact opiate abuser. With more impaired polydrug abusers, however, there is reason to believe that these techniques are countertherapeutic (that is, contraindicated). Experience indicates that the high-severity patient is often younger, uses fewer opiate but more nonopiate drugs, and has fewer social and personal supports than do the patients for whom this modality was originally designed. For these patients, the stresses of community living, the absence of potentially appropriate medication, and particularly the group encounter therapy may be counterproductive. This negative relationship between treatment duration and percent improvement has not been found among the high-severity alcoholic patients treated in the alcohol TC. However, it is significant that the alcohol TC does not employ group encounter techniques, does not mete out embarrassing punishments, and approves a more liberal use of psychotropic medications during treatment (McLellan et al. 1984).

Optimizing Treatment Within the Methadone Maintenance Modality

The results of the comparative study indicated that MM was potentially more effective with the DDSA patient than was the TC. It was recognized, however, that even this level of performance was less than satisfactory. An attempt was therefore made to determine whether services might be added to the MM program that could be of special benefit to these patients. To this end, a study was designed to measure the potential benefits of adding professional psychotherapy to existing drug counseling services within the MM program. In this study, opiate-dependent veterans were randomly assigned to receive supportive-expressive psychotherapy and counseling, cognitive behavioral psychotherapy and counseling, or drug counseling alone (Woody et al. 1983, 1984). All therapy was provided weekly by trained, supervised

professionals over a 24-week period. Drug counseling was provided by rehabilitation workers with bachelor's degrees and an average of 8 years of experience in the drug abuse field.

The working hypothesis was that the psychotherapy would reduce drug use and improve overall patient functioning by reducing the intensity of the psychiatric symptoms. To test this hypothesis, data on the first 62 patients to complete therapy were examined; patients were divided into 3 groups by their ASI ratings of psychiatric severity determined at intake. This provided a valid estimate of general psychological status. On this basis, two 21-subject groups were selected showing high or low levels of psychiatric symptoms. The midrange subjects were excluded to provide the best chance to test the hypothesis. These groups were subdivided by diagnosis and treatment: 10 high-severity subjects receiving counseling, 11 high-severity subjects receiving therapy, 11 low-severity subjects receiving counseling, and 10 low-severity subjects receiving therapy. A summary of the psychological test results for these four groups is presented in table 2, which shows clear group differences in the amount of psychopathology.

Pre- to Posttreatment Improvement

Pre- to posttreatment improvement for patients in each group was examined using the ASI. The ASI severity scores and other related items are presented in table 3. As indicated, the high-severity/counseling group showed improvement only in areas that are clearly related to drug use. This might be expected because these patients were on methadone. The low-severity/counseling group demonstrated significant improvement in several areas, indicating that the counselors had a distinctly greater impact on this group than on the high-severity patients. Conversely, the high-severity/therapy group demonstrated significant improvement in several areas equal to that seen in the low-severity/counseling group. The low-severity/therapy group had also improved considerably, perhaps more than the low-severity/counseling group.

Before discussing the potential role of psychotherapy for these patients, it is important to mention a design limitation in this project. Patients treated in the therapy groups saw a helping person (therapist or counselor), an average of 23 times, whereas those in the counseling-alone group saw their counselors an average of 17 times. Thus, the patients in the therapy groups spent almost a third more time with a helping person. This design was deliberately instituted to see whether the addition of professional therapy to counseling services would provide extra benefits. This question was the major practical issue addressed by the project. It was not considered reasonable that therapists could replace counselors; however, it may be practical—and even cost-effective—for psychotherapy to supplement the important role of counselors with certain patients.

Despite the design limitations, the results of this study indicated that traditional drug abuse counseling provided significant benefit to the low-severity patients. In fact, the overall results for the low-severity/counseling patients were comparable to those for the low-severity/therapy patients. However, the data also indicate that counseling alone was only marginally effective with high-severity patients, despite their receiving significantly higher average doses of methadone. The supplemental therapy provided significant benefit to the high-severity patients, especially in the areas of drug abuse, legal status, and psychiatric function.

Given the favorable results of adding psychotherapy to drug counseling, it is interesting to speculate about why it had this effect. One significant factor was probably the development of an important relationship between patient and therapist. Researchers in the field have theorized that drug dependence is a substitute for significant personal relationships. The benefits shown, however, were probably more than simply the results of developing a relationship as such. Observations suggest that the

TABLE 2. Psychological Status and Treatment Assignment of Groups at Start of Survey

	High Severity With Counseling (N=10)	Low Severity With Counseling (N=11)	High Severity With Therapy (N=11)	Low Severity With Therapy (N=10)
Beck	18	10	21	9
Maudsely-N	41	24	37	20
Shipley IQ	100	102	96	104
Shipley CQ	80	87	80	94
ASI Psychiatric Severity	5.1	2.7	5.6	2.3

benefits of therapy were the result of the ability to form a relationship combined with expertise in using it therapeutically. Many of the counselors form good patient relationships but have trouble managing them, especially with very disturbed patients. As with other patients who have been treated with psychotherapy, the DDSA patient has significant psychiatric problems, especially depression and anxiety. To the extent that drug use is an attempt to medicate these problems and to the degree that psychotherapy can reduce them, psychotherapy can reduce drug use indirectly.

Part two of this chapter has focused primarily on a review of a 7-year program of research at the Philadelphia Veterans' Administration Medical Center investigating DDSAs. This body of research suggests several conclusions. Patients with clear and concurrent problems of drug dependence and one or more other psychiatric disorders represent approximately 15 to 30 percent of the primary psychiatric and primary drug-dependent patient populations in the Philadelphia setting in question (Alterman 1984; Meyer 1985; Mirin 1984; Pickens and Heston 1979).

Evidence from early studies indicates that the sustained, regular use of nonopiate drugs has been associated with long-term psychiatric illness that did not remit even a year after detoxification (McLellan et al. 1979b). Specific patterns of drug use were associated with particular psychiatric disorders. For example, stimulant abuse was associated with mania and psychosis. The recent increase in the use of high-potency cocaine in the free base (crack) form may elevate the proportion of high-severity patients in future years. Depressant abuse was associated with depression and cognitive impairment (McLellan et al. 1979a; McLellan and Druley 1977). It is uncertain whether the regular concurrent use of opiates, alcohol, and cocaine, which now appears to be a common pattern for a significant segment of the drug-abusing population, will result in a particular pattern of psychiatric symptoms and whether that pattern will increase in severity with sustained use.

Severity of the psychiatric condition at program admission seems to be the best overall predictor of response to drug abuse treatment (McLellan et al. 1983a,b). DDSAs show less improvement during treatment and much poorer outcome after treatment than other patients, regardless of treatment modality (Laporte et al. 1981; McLellan et al. 1981).

Given the available drug abuse treatment options, data indicate that MM is more effective than inpatient, drug-free TC treatment of DDSAs, but only for those patients eligible for either option (McLellan et al. 1984). This may be partly due to the stabilizing effect

TABLE 3. Pre- and Posttherapy (7-Month) Improvement

	Problem Severity							
	High Severity With Counseling (N=10)		Low Severity With Counseling (N=11)		High Severity With Therapy (N=11)		Low Severity With Therapy (N=10)	
	Pretherapy	Posttherapy	Pretherapy	Posttherapy	Pretherapy	Posttherapy	Pretherapy	Posttherapy
Medical severity	3.1	2.4	1.7	3.2	2.5	3.5	1.8	0.7
Days with medical problems	4	2	2	4	3	3	1	1
Employment severity	4.5	4.6	5.1 +	3.2	3.8	3.0	3.9 +	2.7
Days worked	9	11	10	13	7	10	9	13
Money earned	272	306	242 +	380	309 +	482	318 *	523
Abuse severity	5.7 +	3.8	3.8 *	1.4	4.9 +	3.0	4.0 *	1.4
Days drunk	4	2	2	1	3	2	2	0
Days of opiate use	6	3	10 *	2	5	2	8 +	3
Days without opiate use	10	8	4	2	7 +	3	3	1
Money for drugs	430 *	190	164 *	47	344 *	65	188 *	8
Legal severity	3.1	3.0	4.5 +	3.1	2.8 +	0.7	2.0 +	0.8
Days of criminal activity	6	3	10 +	4	5 +	0.8	1	0.4
Illegal income	216	181	506 *	300	186 *	43	166 *	10
Psychological severity	5.1	4.8	2.7	1.8	5.6 +	3.0	2.5 +	1.0
Days with psychiatric problems	17	13	8	3	15 +	8	4 +	1

*p<0.01
+p<0.05

of the methadone schedule and the possible antidepressant or antipsychotic effects of methadone. It may also be partly due to the unsuitability of encounter therapy and the patient self-governance interventions used by therapeutic communities with this population. There are no data at this time suggesting that one or the other of these options is generally better across the full range of substance abuse patients applying for treatment.

Although MM combined with regular counseling and a full program of medical and social services appears to produce some benefits for the DDSA client, this is usually at high cost in staff time and energy. Even then, results are less than satisfactory. The present authors have found that DDSA patients are easier to manage and can show significant improvement when weekly professional psychotherapy sessions are added to the existing program of services. For these patients, the addition of professional psychotherapy over a 6-month period was associated with significant reductions in drug abuse, illegal activity, and psychiatric symptoms (Woody et al. 1983, 1984).

Brief psychological assessment of drug-dependent patients at admission may be useful for differentiating patients who are likely to show sustained benefit from traditional counseling from those who are not. The present data indicate that, despite some modest improvement shown by DDSAs in conventional treatment settings, their 6-month outcomes show that they are likely to relapse and to require rehospitalization. It must therefore be concluded that primary drug abuse counseling and rehabilitation, as offered in conventional MM or TC settings, are not adequate to bring about enough change to make self-support likely. Drug-dependent patients with more severe psychiatric problems require more focused and independent inter-

ventions that address their psychopathology directly through appropriate medication and psychotherapy. Drug abuse rehabilitation programs may be a valuable first step in the extended treatment of these patients. By stabilizing drug abuse and improving the general adjustment of DDSAs, such programs may provide the necessary prerequisites for effective assessment and subsequent conjoint treatment of the psychiatric problems found in this growing population.

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AIDS AND INTRAVENOUS DRUG ABUSE

INTRODUCTION

The epidemic of human immunodeficiency virus (HIV) is one of this century's most serious public health challenges. Acquired immunodeficiency syndrome (AIDS) represents the end-stage illness associated with HIV infection. It is characterized by a persistent, severe suppression of the body's immune system, which is responsible for fighting infections. As a result of this profound immunosuppression, persons who have AIDS succumb to a host of opportunistic infections and malignancies. The fatality rate among AIDS patients is high. By January 1990, more than 117,000 cases had been reported in the United States; more than 58 percent had already died (Centers for Disease Control (CDC) 1990). Among the first 5,833 cases reported in New York City, only 15 percent survived for 5 years following their diagnosis (Rothenberg et al. 1987).

During the first 10 years following exposure, the outcome of HIV infection varies from an absence of symptoms, to mild or severe symptoms (AIDS-related complex, or ARC), to profound immunosuppression resulting in the life-threatening infections and malignancies characteristic of the full-blown syndrome (AIDS). The reason for such differences in outcome of HIV infection is that the risk for symptomatic disease probably increases over time after initial infection with the virus. Prospective studies of seropositive homosexual and bisexual men, hemophiliacs, transfusion recipients, and intravenous drug abusers (IVDAs) suggest that the risk of AIDS is low during the first few years following infection and increases substantially thereafter (Lifson et al. 1988; Goedert and Blattner 1988). Several studies have projected that the majority of persons infected with HIV will eventually develop AIDS; however, behavioral cofactors, genetic or host-specific factors, and antiviral therapy of infection may influence this risk for disease progression (Lifson et al. 1988).

In 1986, the Public Health Service made an early forecast that by 1991 more than 270,000 AIDS cases would be diagnosed in the United States. Furthermore, it was anticipated that more than 74,000 of those would occur in 1991 alone (Coolfont Report 1986). By January 1990, slightly more than 117,000 AIDS cases had been reported in the United States (CDC 1990). While this figure is much lower than the projected one, it is not cause for optimism about the severity of the AIDS epidemic. There is very likely a significant under-reporting of AIDS cases. The rate of increase of the number of reported cases is an indicator of this: The increase was 8 percent in 1988 and 25 percent in 1989. Since the drug azidothymidine (AZT) delays the seroconversion of HIV infected individuals from AIDS negative to AIDS positive, some small decrease in the number of AIDS diagnoses may be attributable to it. It is also possible that the less-than-expected number of cases reflects some of the effects of prevention programs. All these factors underline the difficulty of making accurate projections of the proportions of the problem. Projections released in 1988 by the Presidential Commission on the Human Immunodeficiency Virus Epidemic reveal that almost 500,000 American will have died from or progressed to later stages of the disease by 1992 (Presidential Commission on the Human Immunodeficiency Virus Epidemic 1988).

Neither the current nor the projected number of diagnosed cases of the syndrome reflects the enormity of the public health problem presented by this virus. The typical time between infection and the development of symptomatology required for a diagnosis of AIDS was previously believed to be 3 to 6 or more years (Peterman et al. 1985; Lui et al. 1986). More recent studies have estimated this period to be 10 or more years (Bacchetti et al. 1989; Greatbatch and Holmes 1989). Most of the persons expected to develop AIDS between now and 1992 are already infected with the virus. In 1986, the CDC estimated that between 1 and 1.5 million Americans had been infected with HIV and that most of them were unaware that they had been infected (Coolfont Report 1986). The CDC is still using this same estimate of 1 to 1.5 million HIV-infected persons, but there is evidence that this figure may be far too low (St. Louis et al. 1990).

Unlike many other viral infections, HIV infection does not appear to be cleared by the body's immune system. Thus, unless effective therapies are developed, people with HIV will be both infected and infectious for the rest of their lives. No cure for AIDS or vaccine to prevent HIV infection is currently available or expected in the near future.

Existing therapies are limited to treatments for the opportunistic infections and cancers resulting from immunosuppression, experimental drugs used to strengthen the damaged immune system, and antiviral therapies to fight the underlying HIV infection.

At this time, azidothymidine (AZT), also known as zidovudine or Retrovir, is the only drug approved by the Food and Drug Administration (FDA) for the treatment of AIDS and severe ARC. AZT is not a cure for AIDS, nor does it prevent the development of new

infections. However, for some, it slows the disease's progression and improves the patient's quality of life. Unfortunately, AZT is very toxic (Richman et al. 1987); about half of the patients who are treated with it experience bone marrow suppression severe enough to require blood transfusions. The recent suggestion that certain variant strains of HIV may be resistant to treatment with AZT (Larder et al. 1989) gives special urgency to the development of additional antiviral therapies.

Because none of these therapies cures AIDS or clears HIV infection permanently, the prevention of HIV infection has been the primary objective of public health initiatives designed to decrease the further spread of the virus and to mitigate the ultimate consequences of the AIDS epidemic.

Among the numerous agencies within the Public Health Service that have increased the resources spent on AIDS-related problems, the National Institute on Drug Abuse (NIDA) has an important role due to the relationship between intravenous drug abuse and AIDS. The remainder of this chapter will address substance abuse-related issues associated with AIDS and describe this aspect of the Government's response to the epidemic.

AIDS AMONG INTRAVENOUS DRUG ABUSERS, THEIR SEXUAL PARTNERS, AND THEIR CHILDREN

It is estimated that more than one million Americans are intravenous drug abusers (Schuster 1988). Published reports of AIDS among IVDAs first appeared in 1981, about the same time as initial reports of cases among homosexual men (Masur et al. 1981). Currently, IVDAs are the second largest group to have developed AIDS in the United States, and the number of IVDA cases of AIDS is continuing to grow in epidemic proportions. As of January 1990, 21 percent of the more than 117,000 cumulative cases of AIDS among adults were IVDAs, and another 7 percent were IVDAs who also reported homosexual or bisexual involvement, which represents an additional risk for infection (CDC 1990).

As early as 1982, intravenous drug abuse was the major risk factor among 13 percent of New Yorkers diagnosed with AIDS. By 1986, this proportion had risen to 36 percent, almost a 300 percent increase (Weinberg and Murray 1987). The first wave of reported AIDS cases among IVDAs was concentrated within the New York metropolitan area, but cases have now been reported in all 50 States, the District of Columbia, and Puerto Rico.

Black and Hispanic IVDAs account for 51 percent and 30 percent of the cases associated with intravenous drug abuse, respectively (Curran et al. 1988). It is not clear if race-specific factors play a contributing role in the greater numbers of IVDA-associated AIDS cases among members of minority groups. The reported national cumulative incidence of AIDS diagnoses among minority groups has not been adjusted to reflect the racial compositions of the municipalities where the greatest numbers of IVDA cases reside. However, disproportionate rates of HIV infection among Puerto Rican IVDAs and Black IVDAs have been reported in some cities (Chaisson et al. 1989; Lange et al. 1988; Wiebel et al. 1988).

IVDAs place two other groups at risk for developing AIDS: their sexual partners and their children. More than 5,630 AIDS cases attributed solely to heterosexual transmission have been reported among U.S.-born men and women; about half are associated with sexual transmission of HIV from an IVDA (CDC 1990). Nationally, nearly 60 percent of pediatric AIDS patients contracted HIV through perinatal transmission from an IVDA mother or a mother whose sexual partner was an IVDA (CDC 1990). The most rapid increases in the number of AIDS cases are occurring among heterosexuals (figure 1) and children (figure 2). In New York City, where the incidence of HIV infection among IVDAs is greatest, the role of intravenous drug abuse in the heterosexual transmission of HIV is most obvious: 93 percent of

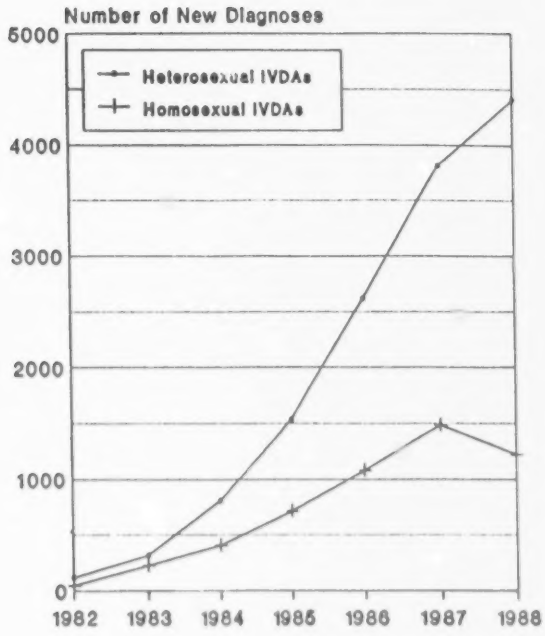

FIGURE 1. IVDA-Associated AIDS Diagnoses in the United States. Each Fiscal Year ends August 31 of that calendar year.
SOURCE: Centers for Disease Control.

heterosexually acquired infections are associated with an IVDA partner, and 80 percent of the pediatric patients have an IVDA for a parent (DesJarlais and Friedman 1988).

HIV-Associated Mortality Among Intravenous Drug Abusers

Current AIDS surveillance data may significantly underestimate HIV-associated mortality and morbidity among IVDAs. Mounting evidence suggests that the strict case definition of AIDS developed by the CDC substantially underestimates the extent of mortality among HIV-infected IVDAs resulting from other infectious diseases (Selwyn et al. 1988b; Stoneburner et al. 1988). A review of "narcotics-related" deaths between 1978 and 1986 among New York City residents indicated substantial increases in non-AIDS mortality. From 1981 to 1986, such deaths increased an average of 36 percent per year, from 472 in 1981 to

FIGURE 2. Cumulative AIDS Incidence Among Children in the United States. Data were reported to the Centers for Disease Control (provisional data through July 1987) by half-year of diagnosis for four exposure groups. Children born to drug-using or sexual-contact mothers are at highest and increasing risk, whereas transfusion-associated pediatric AIDS has been decreasing since the screening of donated blood for HIV antibodies was initiated in the spring of 1985.
SOURCE: DeVita, V.T.; Hellman, S.H.; and Rosenberg, S.A., eds. ***AIDS: Etiology, Diagnosis, Treatment, and Prevention***, 2d ed. Philadelphia: Lippincott 1988. Reprinted with permission.

1,996 in 1986. Infectious diseases accounted for a large proportion of this increase. A review of these deaths, including those that occurred in a cohort of IVDAs, suggested a causal association with HIV infection (Stoneburner et al. 1988). If HIV-associated mortality were readjusted to account for these excess deaths, more than half (53 percent) of the AIDS-related deaths in New York City would involve IVDAs, making IVDA association the largest risk factor for AIDS, even greater than bisexual or male homosexual involvement (Joseph 1988).

HIV-Associated Morbidity Among Intravenous Drug Abusers

In addition to the reported increase in non-AIDS mortality, HIV infection may also be the cause of substantial increases in morbidity among IVDAs, particularly from viral hepatitis. The sharing of needles has long been associated with a high risk of infection with the hepatitis B virus. The normal immune response to hepatitis B exposure is impaired among HIV-infected persons, leading to a higher risk of chronic, perhaps lifelong, infection (Hadler 1988), which may carry an increased risk of cirrhosis and cancer of the liver. It may also mean that a greater number of IVDAs will be able to transmit hepatitis B to others—by sharing injection equipment, sexually, and perinatally. An even more virulent form of hepatitis, delta, is also a risk among IVDAs chronically infected with hepatitis B (Novick et al. 1988). A vaccine is currently available for the prevention of hepatitis B infection, and efforts to increase its availability to IVDAs may be more warranted now than ever.

SEROPREVALENCE OF HIV AMONG INTRAVENOUS DRUG ABUSERS

Many IVDAs are at increased risk for HIV infection because they so often share contaminated injection equipment. Evidence of infectious spread within this population was first noted among diagnosed AIDS cases and subsequently through serological tests, which measure antibodies to viral proteins. These tests, first licensed for use in March 1985, have substantially enhanced the capability to estimate the magnitude of the epidemic among IVDAs and to monitor rates of infection within this high-risk population.

Nationally 226,000 (Hahn et al. 1989) to 335,000 (Booth 1988) IVDAs are estimated to be infected with HIV already. The prevalence of HIV infection varies widely by geographic area and by demographic and behavioral subgroup, ranging from 0 percent to about 70 percent (Curran et al. 1988; Hahn et al. 1989). Survey data from more than 18,000 IVDAs tested in nearly 90 studies have consistently shown the highest prevalence rates in major East Coast cities with geographic or close cultural connections to New York City and northern New Jersey (CDC 1987b). However, even within metropolitan areas, HIV infection has been shown to vary considerably by race among IVDAs in drug treatment (Chaisson et al. 1987, 1989), and by social network among active users not in treatment (Wiebel et al. 1988; Raymond 1988).

The relatively lower rates of HIV infection found in some areas of the country must be interpreted with caution. Low rates of seroprevalence in an IVDA subpopulation may reflect an early stage of epidemic progression, but those rates are far from stable and have sometimes escalated dramatically. Because of the long incubation time between HIV exposure and the development of illness associated with the infection, silent "explosions" of HIV infection can occur. Such increases occurred in New York City; Edinburgh, Scotland; Italy; Spain; and Thailand long before drug-associated case reports.

Historical studies of the epidemic in New York City, using serum samples originally collected for other purposes, show a rapid increase in seroprevalence—from virtually 0 percent in 1978 to 29 percent in 1979, and from 44 percent in 1980 to 52

percent in 1981-83 (Novick et al. 1986). In Edinburgh, similar increases were observed among IVDAs, with seroprevalence rising to more than 50 percent in a period of 2 years (Robertson et al. 1986). In Italy, increases from 0 percent to 76 percent were documented between 1979 and 1985 (Angarano et al. 1985). An increase from 11 percent to 48 percent was observed in Spain between 1983 and 1985 (Rodrigo et al. 1985). HIV seroprevalence surveys in Bangkok demonstrated abrupt increases from 1 percent in late 1987 to 15 percent and 43 percent in March and August 1988 respectively (Phanuphak et al. 1989).

Although the number of sampled cases in these studies is small, the studies consistently document the potential for rapid increases in seroprevalence within the drug-abusing population. Further, even in communities with high existing rates of infection, transmission of the virus can continue to raise the toll of casualties. In 1988, the New York State Department of Substance Abuse Services estimated that 8 percent of seronegative IVDAs become infected each year (Joseph 1988).

A few reports have described apparent stabilization of seroprevalence rates or slowing in the rate of new infections among IVDAs in New York City (Des Jarlais et al. 1989c); San Francisco (Watters et al. 1988; Moss et al. 1988), Innsbruck, Austria (Fuchs et al. 1988), and Stockholm, Sweden (Olin and Kall 1988). However, caution is advised in the interpretation of these reports.

"Stabilization" of seroprevalence in cross-sectional samples such as these does not imply the absence of new infections. Longitudinal studies of identified cohorts of IVDAs are necessary to confirm that few new infections are occurring in these communities. The apparent "stabilization" of seroprevalence in these samples is influenced by many factors, including numbers of new infections, reduced entry into drug treatment and deaths among those IVDAs already infected, risk reduction among active injectors, and the entry of new IV drug users into treatment (Des Jarlais et al. 1989). Moreover, these studies may not be sensitive in detecting new infections among subpopulations of IVDAs underrepresented in these samples. Consequently, while these findings may indeed reflect a true slowing of new HIV infections among IVDAs in those communities, in the absence of additional information, apparent "stabilization" of rates from such samples may in fact reflect a rise, a stabilization, or decline in actual seroprevalence. Concordance of multiple samples in these cities drawn from a variety of sites using different study designs will be required to bolster confidence in the interpretation of stabilizing seroprevalence. Since new infections continue to occur, continued AIDS prevention efforts are essential among IVDAs who continue to share contaminated injection equipment.

Given the covert and illicit nature of substance abuse, accurate estimates of the number of IVDAs in any given community, and representative samples of this group, are difficult to obtain. Because of this, experts must rely on estimation and sampling techniques that approximate rather than precisely represent this population. To date, most seroprevalence data on IVDAs have been based on clients of drug abuse treatment facilities. These convenience samples provided the first systematic assessment of infection within the IVDA population.

However, clients in treatment represent only 10 to 20 percent of the estimated 1.1 million IVDAs in this country (Schuster 1988). The extent to which the rates of infection among clients in treatment reflect those in other IVDA subpopulations is uncertain. Current investigations have begun to focus on those at greatest risk for infection, particularly active users not in treatment. These first studies have demonstrated significant differences between convenience samples and those obtained by community-based outreach efforts (Watters 1987; Wiebel et al. 1988; Raymond 1988; McCoy et al. 1989). Significant biases attributable to voluntary participation in HIV serosurveys at sexually transmitted disease clinics and drug treatment facilities have also been suggested (Hull et al. 1988; Schaefer et al. 1989).

FACTORS ASSOCIATED WITH HIV SEROPOSITIVITY

Among IVDAs, the principal risk factor for infection with HIV is not drug abuse, as such, but the sharing of injection equipment ("works") contaminated with infected blood. This association between the sharing of works and HIV infection is now well established. Studies in the New York City area have repeatedly related seropositivity to the frequency of injection (Marmor et al. 1987; Weiss et al. 1985; Schoenbaum et al. 1987). Additional research in California, Illinois, and New Jersey has related seropositivity to both the frequency of injection and the number of persons with whom equipment was shared (Chaisson et al. 1987, 1989; Weiss et al. 1985; Wiebel et al. 1988).

Two related factors may contribute to the particularly rapid transmission of HIV in a community: the sharing of injection equipment across social networks of IVDAs, and a preference for drugs associated with more frequent injection patterns, particularly cocaine. Sharing injection equipment with anonymous partners is commonly associated with "shooting galleries" (places where addicts gather to inject drugs), in which contaminated equipment is often rented and reused. The tendency to frequent shooting galleries has been associated with an increased risk of HIV seropositivity in at least three studies in the New York City area (Weiss et al. 1985; Marmor et al. 1987; Schoenbaum et al. 1987), as well as among cocaine injectors in San Francisco (Chaisson et al. 1989). In Edinburgh, rapid increases in HIV seropositivity coincided with an increase in sharing of rented injection equipment (Robertson et al. 1986).

Cocaine injection, either alone or in combination with heroin, has been strongly associated with a risk of bacterial endocarditis, hepatitis types A and B, and most recently, HIV infection (Chambers et al. 1987; Chambers and Chaisson 1988; CDC 1988b; Lettau et al. 1987; Chaisson et al. 1989). Cocaine is less expensive and more easily obtained than high-quality heroin in most urban areas of the United States today.

Preliminary findings from the National AIDS Demonstration Research (NADR) projects (NIDA 1988) describe the extent to which cocaine has been incorporated into IVDA injection patterns in New York, Chicago, San Francisco, Houston, Philadelphia, and Miami. Over 80 percent of 2,206 IVDAs reported having injected cocaine during the 6 months prior to being interviewed. One in five IVDAs reported the injection of cocaine alone. Almost two-thirds reported having injected cocaine and heroin, either separately or prepared in combination with each other ("speedball"). In contrast, only 6 percent of the sample reported the exclusive injection of heroin.

Recent research in San Francisco has confirmed an association between cocaine injection and HIV seropositivity (Chaisson et al. 1989). In the same study, cocaine injection was linked to an increased frequency of injection and the use of shooting galleries, both of which carry an increased risk of HIV infection. An injection practice known as "booting," in which blood is withdrawn into the syringe following injection of the drug preparation and then reinjected, may result in larger quantities of residual blood being passed between needle sharers (Chambers et al. 1987; Devenyi and McDonough 1988). Finally, the association of cocaine injection with HIV infection may be related to other factors, including the possible immunosuppressive effects of the drug itself (Klein et al. 1988; Chaisson et al. 1989) and the poor hygiene which may accompany patterns of frequent injection (Cohen 1985).

Cocaine injection may be related to the risk of sexual transmission of the virus as well, either directly or indirectly. Directly, by reducing inhibitions, it may contribute to increased unprotected sexual activity with a consequent increase in risk for sexual transmission of the virus (Ostrow 1987; Goldsmith 1988). Indirectly, cocaine may be associated with an increase in sexually transmitted diseases, which may facilitate the acquisition of HIV infection. Cocaine use has been associated with the tenfold increase in heterosexually acquired sexually transmitted diseases in the past 10 years (Goldsmith 1988). Several studies in the United

States and Africa have shown an increased risk of acquiring HIV infection among persons with genital lesions caused by herpes, syphilis, and chancroid (cited in Haverkos and Edelman 1988; Holmes and Kreiss 1988; Holmberg et al. 1989). Thus, as the prevalence of these other sexually transmitted diseases increases, the risk of acquiring HIV from a single exposure may increase as well.

SEXUAL TRANSMISSION

HIV is spread, as other sexually transmitted diseases are, from infected persons to their partners during unprotected sexual contact (without the proper use of a condom). Anyone who engages in unprotected sexual relations with one of the estimated 1.5 million Americans already infected with HIV is at risk of contracting the virus. Heterosexual transmission of HIV both from men to women and from women to men is believed to be the leading route of HIV infection worldwide (Haverkos and Edelman 1988). In the United States, a 1.21:1 male:female HIV seroprevalence rate has been observed among applicants to military service in the areas reporting the highest rates of infection, suggesting that heterosexual activity may be an important mode of HIV transmission in these regions (Burke et al. 1987).

Although the risk of becoming infected through sexual activity appears to increase with the number of exposures to infected partners, there are reports of infection from a single or few encounters (Francis and Chin 1987; Staskewski et al. 1987). Numerous studies have confirmed that the risk to the steady sexual partner of an infected individual is substantial, but considerable variation in the numbers of infected partners across studies suggests that biologic mechanisms may facilitate HIV transmission (Holmes and Kreiss 1988; Holmberg et al. 1989).

The relative importance of sexual exposure as compared to needle sharing in causing HIV infection in IVDAs is not known. Limitations in the CDC classification scheme for recording diagnosed cases of AIDS probably result in underestimation of the number of heterosexually acquired cases (Haverkos and Edelman 1988; CDC 1989). It is known, however, that most heterosexually transmitted cases of AIDS among adults and adolescents in the United States result from sexual encounters with infected IVDAs. More than 70 percent of U.S.-born heterosexual AIDS patients have reported sexual contact with an IVDA (CDC 1989). In New York City, 87 percent of patients with heterosexually transmitted AIDS reported contact with an IVDA partner (Des Jarlais et al. 1988).

Serological testing of IVDAs and their steady sexual partners confirms that the risk of sexual transmission from an infected partner is high. In one controlled study of the non-IVDA heterosexual partners of IVDAs with diagnosed AIDS, 7 of 12 male spouses and 41 of 88 female spouses of AIDS patients showed serological evidence of HIV infection (Steigbigel et al. 1987). Fischl and colleagues (1987) found an infection rate in such partners of about 40 percent. Other studies among the sexual partners of infected hemophiliacs, recipients of blood transfusions, and bisexuals indicate considerable, though variable, risk of infection through sexual activity. Sexual partners of IVDAs may be at even higher risk if they are themselves IVDAs and share contaminated injection equipment (Tirelli et al. 1986; France et al. 1988).

There is a complex interaction between drug abuse and sexual activity. Some heavily addicted drug abusers experience a loss of libido and are not sexually active. Recent data from a prospective study of active IVDAs in Chicago show that the highest rates of infection were among those who were sexually abstinent. Among sexually active research subjects, the likelihood of infection was correlated with increased numbers of sexual partners (Wiebel et al. 1988; Raymond 1988). These data are consistent with two distinct groups of drug users at highest risk for HIV infection: chronic users with diminished libido and heavy users who exchange sex for drugs.

Sexual transmission of HIV associated with substance abuse may also be an indirect consequence of

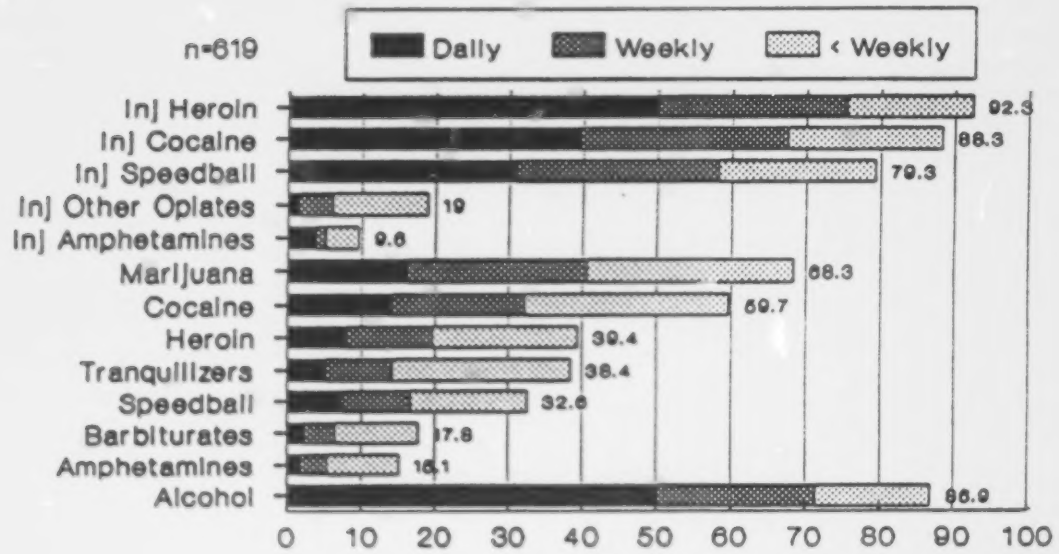

FIGURE 3. Frequency of Use by Type of Drug Used.
SOURCE: University of Illinois at Chicago AIDS Outreach Intervention Project (October 1988).

using intoxicants. An increase in risk for sexual transmission of HIV may result from impaired judgment and reduced inhibition about indulging in unsafe sexual behavior. Studies have established the association between lack of inhibition due to substance abuse and increased unprotected sexual encounters (Stall et al. 1986; Ostrow et al. 1987). For IVDAs, the use of both injected and noninjected substances of abuse may thus contribute to an increased risk for HIV infection. Interviews with active injectors in Chicago indicate that patterns of multiple substance abuse among IVDAs are the norm (figure 3). Drug treatment and AIDS prevention programs will need to take the complexities of such patterns into account (Wiebel et al. 1988).

Both male and female IVDAs who exchange sex for money or drugs are at increased risk of infection through sharing contaminated injection equipment and through unprotected sexual encounters. About half of the street-working female prostitutes in one study acknowledged intravenous drug use (Des Jarlais et al. 1987), and HIV prevalence is three to four times higher among prostitutes who are IVDAs than among those who are not (CDC 1987a).

The potential for heterosexual transmission of HIV from prostitutes to their clients is currently being investigated by NIDA and the CDC. Although there appear to have been relatively few such cases in the United States to date, this potential mode of HIV infection remains a serious concern (CDC 1989).

TRANSMISSION OF HIV INFECTION FROM MOTHER TO CHILD

Predictions of a substantial increase in pediatric AIDS cases between 1986 and 1991 range from the tenfold increase mentioned above (forecast by the Public Health Service), to an approximate fiftyfold increase (10,000 to 20,000 cases) predicted by the National Commission to Prevent Infant Mortality (cited in Presidential Commission 1988). Pediatric

cases are among the most rapidly increasing categories of AIDS cases (figure 2); their number grew from 64 at the end of 1983 to 1,995 by January 1990. Intravenous drug abuse is associated with over half of all pediatric cases: most of these children are born to IVDA mothers, and the additional infants are born to the sexual partner of an IVDA (CDC 1990). Because HIV transmission through the blood supply has been largely prevented through screening methods begun in 1985, the overwhelming proportion of future pediatric AIDS cases is expected to be directly attributable to intravenous drug abuse by a parent.

In 1986, there were an estimated 200,000 women already infected with HIV. Most were at peak childbearing age (13 through 39), and almost all were unaware of their infection (Wofsy 1987). Half of the adolescent women with AIDS in New York City are IVDAs or the sexual partners of IVDAs (Joseph 1988). Ninety percent of mothers of children with AIDS in New York City are Black or Hispanic (Weinberg and Murray 1987). It is estimated that an infected woman has a 20 to 60 percent chance of passing the infection to her child (Presidential Commission 1988). Moreover, pregnancy itself may accelerate the course of HIV disease in the mother, most likely as a result of an altered immune status during pregnancy (Minkoff 1987; Delfraissy et al. 1989; Schafer et al. 1989), though some studies have failed to demonstrate such disease acceleration (Schoenbaum et al. 1989).

In New York City, three of every four children diagnosed as having AIDS have died, most by the age of 3 years (Joseph 1988). Children born with HIV infection have a unique set of problems, sometimes including the need for long-term or permanent hospitalization when other appropriate care settings are unavailable. Infected mothers are often poor and uninsured. Those who seek help for their illness must rely heavily on medicaid and on the availability of services provided by community agencies or public hospitals. Seropositive infants born to addicted mothers often require neonatal intensive care during detoxification. Improved outpatient services and foster care are important elements in the development of cost-effective programs for the treatment of pediatric AIDS in many major metropolitan areas.

COFACTORS IN THE DEVELOPMENT OF HIV AND AIDS AMONG INTRAVENOUS DRUG ABUSERS

Cofactors may influence the likelihood of acquiring HIV infection, and the progression of disease. In addition to the potential cofactors discussed above—the presence of genital ulcers, which may facilitate sexual transmission of the virus, and the altered immune status associated with pregnancy, which possibly may accelerate disease progression in infected pregnant women—it has been postulated that concomitant viral infections could stimulate HIV replication in infected cells (Fauci 1988). Concomitant infections with Epstein Barr virus, cytomegalovirus, hepatitis B virus, or herpes simplex virus may contribute to disease progression in HIV seropositive individuals.

Other factors commonly associated with intravenous drug abuse are suspected of compromising immune function, and thus may serve as cofactors in disease progression. These cofactors include the potential direct immunosuppressive effects of injected substances (Klein et al. 1988); the use of nonsterile drug preparations; poor nutrition; stress; and the use of other noninjected drugs, such as alcohol and marijuana, which may play a role in reducing immunity (Bridge et al. 1988; Des Jarlais et al. 1988). The importance of such cofactors is being investigated in ongoing cohort studies of IVDAs in Baltimore and New York City, sponsored by NIDA and the National Institutes of Health.

PREVENTION OF HIV INFECTION AMONG INTRAVENOUS DRUG ABUSERS AND THEIR SEXUAL PARTNERS

Recent reports addressing the public health threat posed by AIDS have expressed a disconcerting consensus in their interpretations of the epidemic's severity and in their conclusions regarding the scope of responses currently warranted. The Public Health Service, the Institute of Medicine, former Surgeon General C. Everett Koop, the National Research Council, and the Presidential Commission on the HIV Epidemic have all provided projections highlighting the catastrophic potential of the current epidemic and urged an unprecedented mobilization of resources to check further spread of the virus (Coolfont Report 1986; Institute of Medicine 1986; Turner et al. 1989; Koop 1986; Presidential Commission 1988).

Until a large-scale medical intervention becomes available, prevention campaigns promoting risk-reduction measures are the primary means available for moderating the epidemic's impact. Preventing the primary spread of AIDS among IVDAs is also an important component of effective strategies to halt the secondary heterosexual and perinatal spread of the virus to the general population. Heterosexual IVDAs, representing only 17 percent of AIDS cases, appear to be responsible for more than 75 percent of the secondary spread of HIV. The substantial geographic variation in HIV seroprevalence rates, together with the known potential for rapid increases in those rates within a community, indicate the importance of implementing HIV prevention strategies even in areas of relatively low infection rates.

A number of studies suggest that the adoption of sexual risk-reduction measures, such as reducing the number of sexual partners and using condoms with every sexual encounter, lag behind IVDAs' adoption of risk-reduction measures related to needle sharing (Kleinman et al. 1987; Watters et al. 1988; Jain et al. 1989). Unless more effective strategies are identified for encouraging safer sex practices, the challenge of moderating secondary spread through sexual transmission may prove to be more difficult than reducing primary spread through needle sharing.

This section reviews the current levels of AIDS knowledge among IVDAs and sugggests the importance of distinguishing general awareness about AIDS from knowledge of effective needle hygiene and behavioral change. A comprehensive approach to the prevention of AIDS among IVDAs is discussed, including programs that address those who want to stop injecting, those who are unable or unwilling to stop injecting, those who have not yet begun to inject drugs and are at increased risk for starting, and the sexual partners of persons in these groups.

Knowledge of AIDS Among Intravenous Drug Abusers

Some early studies suggested that IVDAs had a high level of general awareness about AIDS, but these studies were performed in areas with the largest numbers of cases. Subsequent studies have shown geographic differences in knowledge among IVDAs and their perception of vulnerability. They indicate continuing misunderstanding and lack of information among large numbers of IVDAs with respect to AIDS and its prevention.

In 1984 and 1985, studies of New York IVDAs in jail and in methadone maintenance programs indicated that over 90 percent had heard of AIDS and knew that intravenous drug use was involved in spreading it (Friedman et al. 1987; Selwyn et al. 1988a). In both of these studies, more than half of those interviewed reported some type of behavior change to reduce their risk of AIDS. Similar results were found among New York City "street" addicts a year later (Kleinman et al. 1987). However, this high level of knowledge was not demonstrated in a 1985 survey of methadone maintenance clients in Detroit, where only 67 percent identified IVDAs as a group at high risk for AIDS and

57 percent were not concerned that they might get AIDS (Williams 1986).

Moreover, general awareness about AIDS among IVDAs should not be confused with possession of the knowledge critical to preventing AIDS. A 1984-85 study conducted in New Jersey methadone facilities indicated that, although the majority of IVDAs had heard of AIDS and its connection with intravenous drug use, only about one-third knew how to disinfect their needles. And over one-third believed incorrectly that those infected with HIV necessarily show symptoms of infection (Ginzburg et al. 1986). The NADR projects have been documenting the substantial national variation in knowledge of effective AIDS prevention behaviors among IVDAs.

Current Studies of AIDS Knowledge Among Intravenous Drug Abusers

A major contribution of the expanded NIDA-sponsored research has been a more accurate assessment of IVDAs' sources of AIDS prevention information. Interviews conducted with over 2,206 IVDAs have indicated that the most commonly reported source of general information about AIDS is television (79 percent). Word of mouth was frequently cited as a source of information about AIDS (21 percent), as were health care facilities (36 percent). However, television was not the source most commonly used for critical information concerning practices to reduce the risk of HIV infection. For this information, the majority of IVDAs relied upon word of mouth on the streets (53 percent). Brochures, fliers, and pamphlets were listed by 42 percent of IVDAs as key sources of needle-cleaning information. Television and newspapers were less often mentioned as sources of this information (NIDA 1988).

These findings and those of ethnographic investigations (Feldman et al. 1989) underscore the importance of employing community-based outreach staff to deliver accurate AIDS prevention information to this population by word of mouth, a recommendation of the National Research Council (Turner et al. 1989). They also establish the continued need for culturally sensitive educational literature that explicitly outlines appropriate risk reduction practices. Some programs still lack educational material appropriate for distribution to members of minority groups and women at risk for IVDA-associated AIDS.

AIDS PREVENTION THROUGH EXPANDED DRUG TREATMENT

Need for Expanded Drug Treatment

Treatment for problems of drug dependence generally includes drug detoxification, methadone maintenance (specifically for addiction to opiates), drug-free counseling in outpatient settings, and drug-free counseling in residential settings. In 1988, treatment "slots" were available for only about 148,000 of the estimated 1.1 to 1.5 million IVDAs in the United States (Schuster 1988). AIDS has led to a dramatic increase in the number of IVDAs desiring treatment. Rapid expansion of drug treatment capacities has been recommended by the Public Health Service, the National Academy of Sciences/Institute of Medicine, the National Research Council, and the Presidential Commission on the HIV Epidemic (Coolfont Report 1986; Institute of Medicine 1986; Turner et al. 1989; Presidential Commission 1988).

In a 1987 NIDA survey of 12 methadone maintenance facilities in Connecticut, Florida, Georgia, Illinois, and New Jersey, all but one had waiting lists (Gottlieb 1988). New York and New Jersey have increased treatment capacities to meet new demands, but the 3,000 additional treatment places created in mid-1987 were immediately filled and 1,000 IVDAs were placed on waiting lists. The creation of an additional 5,000 places by mid-1989 was recommended (Des Jarlais and Friedman 1988). In response to these needs, Federal, State, and local funding has been in-

creased to a total of well over $2 billion annually to treat drug addiction (ONDCP 1990).

Fear of AIDS continues to be a major factor contributing to the increased demand for treatment. In New Jersey, community health outreach workers distributed vouchers for free drug detoxification to encourage entry into treatment. More than 80 percent of these vouchers were redeemed (Jackson and Rotkiewicz 1987).

Community-based AIDS prevention for active IVDAs shows promise for recruiting clients who have no previous experience with the drug treatment system (Kleyn et al. 1989). Of the more than 1,700 active injectors recruited for study in NIDA projects based in Chicago, Denver, El Paso, Baltimore, and San Francisco, over 60 percent indicated in interviews that they had no prior history of methadone maintenance therapy (Lampinen et al. 1989).

Efficacy of Drug Treatment as an AIDS Prevention Measure

The effectiveness of drug abuse treatment as an AIDS prevention strategy is suggested by several lines of evidence. First, methadone maintenance treatment reduces the frequency of opiate injection (Ball et al. 1988; Hubbard et al. 1988; Chaisson et al. 1989) and thus the occasion for sharing of injection equipment. Second, prior or current enrollment in drug abuse treatment is associated with a reduced risk of HIV seropositivity (Novick et al. 1986; Hartell et al. 1988). Third, a reduced risk of HIV infection is associated with methadone treatment compliance (Blix and Gronbladh 1988). And fourth, longer duration in treatment has been associated with a reduced risk of HIV infection in multiple studies (Brown et al. 1988, 1989; Novick et al. 1988, 1989; Blix and Gronbladh 1988).

However, entry into drug abuse treatment is not a perfect AIDS prevention strategy. Relapse to intravenous drug abuse is common among patients who leave treatment prematurely, regardless of the treatment modality. In one study, four out of five patients (82 percent) who remained in treatment less than 1 year returned to their addiction (Ball et al. 1988). In addition, some clients, even in treatment, continue to inject intermittently (particularly cocaine), though much less often than prior to entering treatment (Ball et al. 1988; Chaisson et al. 1989). Given the patterns of multiple drug abuse that appear to be the norm among IVDAs, methadone treatment programs need to address the potential abuse of nonopiate substances, both legal and illicit, during the course of treatment.

Variation in treatment outcome, as measured by intravenous drug abuse, has been found among outpatient methadone maintenance, residential drug free, and outpatient drug free programs (Hubbard et al. 1988). In one study, this variation was not attributable to client characteristics but to the programs themselves (Ball et al. 1988). Superior treatment outcomes were related to high patient retention rates, positive relationships between clients and staff, and low staff turnover. Considering these differences, quality of care must be taken into account in plans to increase treatment capacity in response to the growing epidemic of HIV infection.

Studies to evaluate the efficacy of drug treatment programs are the subject of continuing NIDA research. In fiscal year 1989, NIDA devoted $30 million to research designed to reduce illicit drug abuse during the course of treatment, treatment dropout rates, and relapse following treatment. Special emphasis has been placed on the inclusion of women and members of minority groups in these treatment research projects. Some women have experienced difficulty in entering drug abuse treatment because they require child care for children at home: increased availability of child care must accompany increased availability of treatment. Overcoming treatment problems is expected to make drug abuse treatment an even more effective AIDS prevention strategy.

RISK REDUCTION FOR ACTIVE INTRAVENOUS DRUG ABUSERS

Drug abuse treatment programs must be expanded to accommodate the growing numbers of addicts interested in entering treatment, but such expansion will not be sufficient to control the HIV epidemic among IVDAs. Even if treatment capacity were unlimited, experience to date suggests that, at any given time, most active drug injectors are not interested in entering drug treatment. Some addicts new to treatment continue to use drugs on a sporadic basis, and other clients relapse.

If the rapid spread of HIV among IVDAs is to be slowed, current prevention efforts must include promotion of effective needle hygiene and other risk-reduction measures for those IVDAs who are either unwilling or unable to stop injecting. Most responsible risk-reduction campaigns emphasize the primary message that the best way to avoid HIV infection is to stop injecting completely. They also recommend the elimination of needle sharing and in accordance with the recommendations of the National Research Council (Turner et al. 1989), provide explicit instructions for disinfecting injection equipment for those who do not stop injecting. The inclusion of information about the risks associated with needle sharing in education programs has been considered essential by former Surgeon General C. Everett Koop (1986) and the Presidential Commission (1988) on the HIV Epidemic. To increase the likelihood of behavior change, many programs include the distribution of disinfectants such as bleach, which has been shown to be both an effective disinfectant for inactivating HIV (Resnick et al. 1986) and relatively nontoxic (Froner et al. 1987).

Community-based outreach educators have been effective in reaching active IVDAs and providing them with the information and means to reduce their risk of contracting or spreading HIV. Further, if allowed to establish an ongoing presence in the community, outreach workers are able to maintain high levels of AIDS awareness and reinforce the adoption of risk-reduction measures.

Some prevention programs have been able to demonstrate reductions in the frequency of injection and needle sharing, increases in treatment referrals, and increases in the sterilization of injection equipment among IVDAs who continue to share works. Evaluations of the effectiveness of these programs are still in progress. However, published reports have consistently indicated that IVDAs have a high level of concern about AIDS and take steps to reduce risk when they are provided with the means for change (e.g., condoms and bleach) and when those changes are supported in a sustained manner within the community.

A San Francisco program begun in July 1986 demonstrates that dramatic increases in risk reduction can occur among IVDAs entering treatment as well as those interviewed on the street (Chaisson et al. 1987; Watters et al. 1988). In addition to distributing bleach and instructing IVDAs in its proper use, the program employed neighborhood posters and billboards to promote its risk reduction message. In 1985, only 6 percent of those who shared needles reported that they usually or always sterilized with bleach. In 1987, this figure had increased to 47 percent, and by 1988, to over 70 percent. Concomitant decreases were noted in the percentages of persons reporting that they never used bleach (from 76 percent in 1986 to 30 percent in 1988).

The most important indicator of the effectiveness of these intervention projects will be a reduction in the number of new HIV infections in these targeted populations. NIDA is currently sponsoring evaluations of identified cohorts of IVDAs with periodic HIV antibody testing.

Programs that exchange sterile syringes and needles for used ones at no cost have been introduced in a number of European cities and in Australia. Pilot programs have been initiated in New York City; Portland, Oregon; Boulder, Colorado; and Tacoma, Washington; others have been proposed in New Jer-

sey, Massachusetts, and California. Evaluations of the syringe exchange programs in England and Scotland (Hart et al. 1989; Stimson et al. 1989), Amsterdam (Hartgers et al. 1989), New York City (Des Jarlais et al. 1989b), and Tacoma (Hagan et al. 1989) are still in progress. Preliminary reports have suggested that there are modest reductions in the frequency of needle sharing among participants following entry into the exchange program. The data do not support the contention that participation in the exchange results in increased frequency of injection. On the other hand, the drop-out rate from most programs is very high, enrollment is low, and studies in the United Kingdom and Amsterdam indicate those most likely to be sharing needles ar also less likely to enrolling the first place (Stimson 1989). although there are some encouraging reported changes in needle sharing behavior, it remains to be seen whether needle exchange programs have a significant impact on the spread of HIV infection among IVDAS, their sex partners, and their children.

AIDS PREVENTION FOR DRUG ABUSERS WHO DO NOT INJECT DRUGS

The rapid increase in the prevalence of HIV infection among IVDAs has led to a dramatic increase in the risk of transmission to new intravenous drug abusers. Efforts to prevent intravenous drug abuse have thus far been limited to broad-based television and print media campaigns. Difficulty in identifying the demographic and behavioral factors that place current substance abusers at high risk of initiating intravenous drug abuse does not preclude the implementation of a targeted AIDS intervention program by public health officials. Prevention efforts can be addressed to high-risk noninjectors whose friends inject.

To accomplish this, AIDS information can be incorporated into existing drug abuse prevention campaigns in schools, family groups, community organizations, and broadcast and print media. Because many persons at increased risk of beginning to use intravenous drugs may already have left school, these efforts cannot rely on school-based programs alone. Community-based outreach efforts can address social networks of drug abusers that include noninjectors, particularly cocaine users.

However, based on the experience of other risk reduction programs, it is unlikely that a single session of AIDS education will suffice to prevent the transition from nonintravenous to intravenous drug abuse. The findings of one such intervention study in New York City suggested the inadequacy of such an approach and the importance of close personal relationships with drug injectors in mediating this transition (Des Jarlais et al. 1989a). Clearly, attention to the complex behavioral determinants of the initiation of intravenous drug abuse will be required in order to design effective intervention strategies for this population.

PREVENTING THE SEXUAL TRANSMISSION OF HIV

Monogamous relationships, sexual abstinence, and the use of latex condoms by the sexually active are the most effective measures for reducing sexual transmission of HIV. Recommendations for proper condom use have been published (CDC 1988a). Condom use is associated with a reduced risk of HIV infection among the sexual partners of infected individuals in the United States (Fischl et al. 1987; Mann et al. 1987) and among prostitutes in Africa and Greece (Ngugi et al. 1988; Roumeliotou et al. 1988).

A substantial proportion of the female sexual partners of male IVDAs do not use intravenous drugs but are at high risk for sexual transmission of HIV. Providing AIDS education to these women is a challenge, not only because they are difficult to reach, but also because economic and social disadvantage contributes to their inability to adopt sexual risk-reduction techniques. In fiscal year 1988, NIDA sponsored an outreach program for partners of IVDAs. Demonstra-

tion projects based in Los Angeles, Phoenix, and Boston aim to reach both non-IVDA partners and prostitutes through outreach. The culturally sensitive educational techniques being explored emphasize the use of appropriate language and employ community role models.

HIV TESTING AND COUNSELING OF INTRAVENOUS DRUG ABUSERS AND THEIR SEXUAL PARTNERS

Prevention research indicates that HIV antibody testing should be considered an adjunct to, rather than a substitute for, intensive counseling efforts. Increased availability of voluntary and confidential HIV testing and counseling of IVDAs and their sexual partners has been recommended by the Public Health Service (Coolfont Report 1986), the National Academy of Sciences (Institute of Medicine 1986; Turner et al. 1989), and the Presidential Commission on the HIV Epidemic (1988). Additional prevention research is needed to determine whether any benefit is gained by expanded testing and the circumstances under which counseling and testing optimally contribute to increased risk reduction among IVDAs.

Additional funding will be needed to support increases in HIV counseling and testing services at drug treatment facilities. One study in a New York methadone maintenance program estimated that the addition of voluntary testing and counseling will require a decrease in the staff:client ratio from 1:50 to 1:35 (Curtis et al. 1989). This need for increased staff and concomitant staff AIDS training is in addition to the staff and training increases required for expanded treatment itself. Counseling and testing services should be coordinated with referrals for adequate medical and psychosocial care of seropositive clients.

Regardless of the setting in which such counseling and testing occurs, IVDAs and their sexual partners who remain at continued risk of exposure to HIV (through either needle sharing or unprotected sexual relations) should be encouraged to undergo periodic retesting. In Chicago, a retrospective study of IVDAs who sought anonymous HIV antibody testing between December 1985 and March 1988 indicated that fewer than 2 percent were retested at those sites (Lampinen, unpublished data).

THE SPECIAL CARE NEEDS OF HIV-SEROPOSITIVE INTRAVENOUS DRUG ABUSERS AND THEIR PARTNERS

Despite the success of future prevention efforts, an estimated 226,000 (Hahn et al. 1989) to 335,000 IVDAs (Booth 1988) already are infected with HIV (Booth 1988) and many will progress to symptomatic illness. Seropositive and symptomatic IVDAs have special care needs that distinguish them from other patients with AIDS and HIV-associated disease.

Long-term resource requirements for clinical care and social services continue to be major concerns for those who treat HIV-seropositive IVDAs (Joseph 1988; Weinberg and Murray 1987). These concerns have prompted numerous calls for innovative approaches to providing medical treatment through outpatient clinics and in community settings in order to reduce unnecessary hospital stays. Community-based programs will substantially reduce the medicaid burden attributable to HIV-related illness. NIDA and the Health Resources and Services Administration are jointly sponsoring a series of case management studies to examine the use of case management as a method for linking drug treatmetn services and HIV treatment services. The goals of the studies are to improve the comprehensive continuum of treatment services available to HIV-infected IVDAs, to improve the recruitment and retention of this population to treatment and, ultimately, to reduce the likelihood that these individuals will continue to contribute to the

transmission of HIV transmission of HIV through illicit drug use.

Homeless Intravenous Drug Abusers

Homeless IVDAs (living on the streets or in shelters) have been noted among both hospitalized patients with AIDS (Torres et al. 1987) and those at increased risk for HIV infection (Wiebel et al. 1989). Community field workers must locate these IVDAs, who pose special problems for both AIDS prevention efforts and medical management. Homeless patients with AIDS may require more intensive medical case management. In one study of homeless AIDS patients, antibiotic therapy for infections was often not completed, and patients sometimes failed to take medications as outpatients because they lost or could not afford to fill their prescriptions. Hospital stays were longer for homeless patients (Torres et al. 1987).

Housing of symptomatic HIV-seropositive IVDAs has become a major concern in many urban areas. Residential facilities for homeless persons with AIDS has been shown to be a cost-effective alternative to unnecessary hospitalization. However, in many cases, community-based AIDS residential facilities and emergency shelters are not prepared to house the active IVDA (Hummel et al. 1989).

Psychiatric Aspects of Treatment of Intravenous Drug Abusers Who Have AIDS

In addition to the neuropsychiatric manifestations of HIV infection, health care workers commonly encounter denial, anger, depression, and isolation among AIDS patients. Psychiatric management of these feelings may be useful as part of drug abuse treatment. Drug abuse counselors must develop innovative treatment approaches that emphasize not future possibilities but the preservation of current health (Batki et al. 1988).

Special Needs of HIV-Seropositive Parents

Women with HIV infection tend to be in their peak child-bearing years and have special needs (Wofsy 1987). In addition to the isolation suffered by many AIDS patients, these women may experience grief for the loss of child-bearing potential in view of the risks of perinatal transmission. Women who abuse intravenous drugs often lack sufficient medical care, counseling, and child care. There is a special need for child care services to facilitate the drug treatment, detoxification, and medical care of HIV-infected parents. For seropositive IVDA parents, there may be a need for early legal planning for the future custody and care of children.

TRAINING AND SUPPORT FOR AIDS PREVENTION STAFF

Conferees at the August 1988 meeting of the World Health Organization (WHO) emphasized making basic AIDS training mandatory for all treatment staff. NIDA began extensive training in the United States in 1986 and has served as an adviser to WHO in the development of the training materials. The rapid increases in drug treatment capacity and the introduction of HIV counseling and testing into these facilities will require substantial increases in the numbers of AIDS training workshops and written materials produced by NIDA.

Staff "burnout" is a problem in most AIDS research and service agencies. Outreach workers who are former addicts require psychosocial support, as they may identify closely with their clients. This should include working in pairs as outreach teams, psychological counseling, and group support, as needed.

CONCLUSION

There still exists a "window of opportunity" for the prompt implementation of AIDS prevention programs among IVDAs and their sexual partners. Relatively low rates of infection should be viewed with caution: substantial variation in infection rates has been noted among subpopulations of IVDAs in the same city, and the potential for extremely rapid spread of HIV among needle sharers is now well established. Cocaine use is highly prevalent among IVDAs in the United States and recent studies have associated its injection with an increased risk of HIV infection, particularly among IVDAs who inject frequently and share injection equipment with multiple partners in shooting galleries.

Because secondary sexual and perinatal spread of the virus depends largely on primary spread through needle sharing, prevention efforts specifically for IVDAs promise to have substantial impact in moderating the future course of the epidemic. Increased availability of drug treatment, particularly to members of minority groups and women with children, has been widely recommended.

In addition to the expanded availability of drug treatment, increased efforts to reduce the risk of infection are needed to address the majority of IVDAs who are either unable or unwilling to enter drug treatment at any given time. A substantial body of data indicates that IVDAs not in treatment are both concerned about AIDS and able to reduce their risk of infection through reduced needle sharing, effective needle hygiene, and safer sexual practices. If the spread of HIV infection is to be moderated, additional research will be required to identify the methods best suited for achieving behavioral change in markedly different subpopulations of IVDAs.

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COCAINE AND OTHER STIMULANTS

INTRODUCTION

Central nervous system stimulants come from many naturally occurring and synthetic sources. Naturally occurring stimulants include cocaine (from the coca plant), cathine and cathinone (derived from khat), nicotine (from tobacco leaves), and caffeine (found in coffee beans). Synthetic compounds include amphetamine and its numerous chemically related relatives (i.e., analogs) such as methylenedioxyamphetamine (MDA); 3,4-methylenedioxy-methamphetamine (MDMA); and phenylpropanolamine. Current research on nicotine will not be discussed here, as it is the subject of a separate chapter in this volume.

Although chemical structures and mechanisms of action of central nervous system stimulants differ widely, individual compounds share many properties. They all produce an alerting, mood-elevating, or psychostimulating effect that is dose related.

Intense feelings of well-being and, frequently, of euphoria also occur, as measured by self-report scales and questionnaires.

Stimulants are abused in many ways. However, the increasing popularity of smoked cocaine now offers users an intense "high" without the risks associated with injecting a drug intravenously. In addition, cocaine and other stimulants are often used in combination with other drugs such as alcohol or marijuana. This pattern, called polydrug abuse, is particularly difficult to study and treat because of the complex interactive effects that occur when drugs are combined.

Research has been, and remains, the only way to provide accurate information for understanding, treating, and preventing cocaine abuse. There have been several important developments in stimulant abuse research since 1987. Much of our understanding of the basic mechanism of action, toxicity, and treatment of cocaine abuse has come from laboratory studies using animals. Stimulant research has focused on cocaine because of its increasingly widespread use, profound abuse liability, and significant toxicity. Among the issues to be discussed in this chapter are the epidemiology of cocaine abuse, cocaine and polydrug abuse, the relationship between cocaine use and acquired immunodeficiency syndrome (AIDS), techniques for detecting cocaine in biological fluids, cocaine's toxic effects on the cardiovascular system, treatment for cocaine toxicity, behavioral toxicity, and pharmacological and nonpharmacological strategies for treating cocaine dependence. The results of extensive studies using animal models that have provided a better understanding of the abuse liability and neurotoxicity of the "designer" drug MDMA will be discussed, as well as look-alike drugs and the caffeine withdrawal syndrome.

COCAINE

Epidemiology of Cocaine Use

The National Household Survey on Drug Abuse indicates that cocaine use is widespread across the United States. The latest survey, completed in 1988, indicates that 2.3 million Americans have used cocaine within the last 30 days and that 1.75 million have used other stimulants without a prescription (Johnson 1989). In addition, data from the National High School Senior Survey show that the number of young Americans using illicit drugs increased dramatically from 1975 until 1979; for many drugs, use peaked in 1979 and began to decline through 1988. Cocaine use among high school seniors has decreased slightly each year from its all-time high in 1985. However, even though the use of cocaine has decreased, data from the Drug Abuse Warning Network (DAWN) indicate that of emergency room admissions involving cocaine, those caused by smoked cocaine rose from 6 percent in 1984 to 33 percent in 1988.

The hydrochloride salt is the most common form of cocaine sold in the United States. It is water soluble and is easily absorbed via the nasal mucosa (i.e., "snorting") and can be injected intravenously. After intranasal administration ("snorting"), the onset of cocaine's action occurs within 3 to 5 minutes, with peak subjective effects occurring within 15 to 20 minutes. Peak cocaine levels in blood plasma occur 20 to 60 minutes after nasal inhalation, and decrease gradually over the next hour. After intravenous administration, the most intense subjective effects occur within 3 to 5 minutes, as do peak blood plasma levels. The subjective drug effects disappear within 30 to 40 minutes after injection (Javaid et al., 1978).

Cocaine can also be smoked and the introduction of this method of administration has contributed to an increased use of cocaine. Because the melting and vaporization point of cocaine hydrochloride is so high (195 °C), it cannot be smoked; it must first be

converted to cocaine base which readily vaporizes at 98 ° C.

A few years ago, converting cocaine hydrochloride into its smokable form (i.e., free base) was a dangerous and lengthy process that entailed "cooking" the cocaine in an alkaline solution, such as ammonia or baking soda, and then extracting the base using volatile solvents such as ether. Because ether is highly flammable, this process is extremely dangerous. In contrast, the conversion of the hydrochloride salt into crack (or "rock"), is accomplished using baking soda and water rather than an explosive solvent. Thus, not only is crack much simpler to make, but it is a far safer process to conduct.

As with free base cocaine, crack's onset of effects is almost immediate. Snyder et al. (1988) have demonstrated that the composition of cocaine base smoke is 93.5 percent cocaine particles and 6.5 percent vapor. In addition, the particle size was determined to be 2.3 microns which is small enough to pass freely into the alveolar region of the human lung. It is not surprising that inhaled cocaine reaches the brain about 8 seconds after smoking (Mofenson and Caraccio 1987). Because the free base cocaine produced by both methods is more fat soluble, peak plasma levels and subjective effects are attained almost immediately. However, greater fat solubility also results in a faster redistribution of cocaine from the brain to other fat-containing tissues, thus causing its effects to disappear rapidly (i.e., the "crash").

The selling of crack at low cost in amounts equal to a single dose was an evil stroke of marketing genius that brought the drug into the financial grasp of virtually anyone who wants it. This and the above factors—manufacturing safety and ease of both manufacture and self-administration, plus the unusually rapid onset of effects—have contributed to the proliferation of crack abuse.

It is important to realize that cocaine, crack, and free base cocaine are all the same drug with pronounced subjective effects that are extremely reinforcing. There is no "safer" form of the drug when it comes to abuse potential. It can be argued, however, that crack may be the most pernicious threat because of its fast onset, low cost, and ease of administration.

Cocaine and Polydrug Abuse

Increased cocaine use has also made polydrug abuse a more significant problem. The drug of choice among less affluent individuals used to be alcohol or marijuana, but the new inexpensive forms of cocaine are now gaining popularity in this group. A number of surveys indicate that drug users frequently switch drugs or use them concurrently (Washton and Gold 1986). A particularly popular combination is marijuana and cocaine (Abelson and Miller 1985). Although it still is unclear exactly why individuals use more than one drug at a time, there are several reasonable hypotheses: the second drug may be used to enhance the effects desired from the first drug; the second drug may be used to counteract or reduce undesirable effects believed to be associated with the first drug; or combinations of drugs may be used to achieve a novel effect unattainable from one drug alone. The side effects and potential toxic reactions associated with the use of drug combinations have not been systematically studied and are not well understood. One partial explanation for the increase in cocaine-related toxic reactions may be the increased frequency of its use with other drugs.

Recent studies involving cocaine-ethanol and cocaine-marijuana combinations have shown that the cardiovascular effects of such combinations are more pronounced than when either drug is given alone. The cardiovascular consequences of cocaine-ethanol combinations have been studied in human subjects during a resting state and during performance of a specific task (Foltin and Fischman 1989). Cocaine alone increased both heart rate and blood pressure whereas ethanol alone increased heart rate and decreased resting blood pressure. Combinations of cocaine and ethanol resulted in heart rate increases three to five times greater than when either drug was given alone.

Even greater increases were observed when subjects received both drugs and were required to perform a task.

Foltin and colleagues (1987) have also studied the cardiovascular effects of marijuana and cocaine combinations. Both drugs increased heart rate and blood pressure when taken alone, and the increases after simultaneous use were higher still. Certain combinations resulted in heart rate increases of about 50 bpm and systolic blood pressure increases of 20 mm Hg. Since it is likely that doses higher than those used in this study are taken outside of the laboratory, individuals who abuse marijuana and cocaine simultaneously may be at risk for significant cardiovascular stress. It should be pointed out that the subjects in the experiment were tested under resting conditions. The cardiovascular effects of cocaine are potentiated during mildly stressful situations as subjects complete a specific task (Foltin et al. 1988). These findings may explain several cases of cocaine overdose in athletes who had recently engaged in strenuous physical activity. These studies highlight the importance environmental conditions can have on an individual's response to cocaine and cocaine-marijuana and cocaine-ethanol combinations.

Cocaine and AIDS

In the United States, 28 percent of AIDS patients are intravenous drug abusers (Centers for Disease Control 1989) who may have contracted the human immunodeficiency virus (HIV), which causes AIDS, by sharing needles with infected persons. Although heroin is the drug of choice among intravenous drug abusers, the increase in cocaine abuse in the general population has been paralleled by increased cocaine abuse by heroin addicts (Donohoe and Falek 1988; Kaul and Davidow 1981; Kosten et al. 1987a). These findings are particularly important because the AIDS virus enters the general, non-drug abusing heterosexual population primarily through sexual contact with intravenous drug abusers (Des Jarlais et al. 1988; France et al. 1988; Battjes et al. 1988).

There are other physical and mental health complications associated with AIDS and cocaine abuse. Recent evidence indicates that cocaine may suppress the immune function in both animals and humans (Klein et al. 1988). This means that the body's ability to resist and combat infection such as that associated with HIV is severely compromised. Also, two groups of researchers have identified a specific set of AIDS-related neuropsychiatric complications. AIDS patients exhibit bouts of depression, impaired memory and concentration, agitation, panic attacks, anorexia, tachycardia, seizures, insomnia, delusional thinking, and hallucinations (Faulstich 1987). These may be the result of AIDS or AIDS-related complex or may be a direct effect of HIV on the central nervous system (Perry and Jacobson 1986; Faulstich 1987). In addition, these symptoms are also associated with cocaine abuse and may antedate seropositivity for HIV. Because the symptoms emulate many clearly defined psychiatric disorders, the diagnosis of AIDS may be delayed (Shaffer and Costikyan 1988). As the predicted increase in HIV seropositivity among intravenous drug abusers occurs, the clinician's task of adequately diagnosing patients in treatment settings can be expected to become more difficult.

In reference to the national need for more information about AIDS and drug abuse, the National Institute on Drug Abuse (NIDA) has increased its budget for AIDS research from almost $5 million in 1986 to nearly $140 million in 1990.

Cocaine Toxicity

Detection in Body Fluids

Obtaining accurate measurements of cocaine in body fluids represents a major challenge to the analytical toxicologist and pharmacologist. Not only are blood levels typically low, but cocaine is rapidly metabolized to other compounds because it is susceptible to both enzymatic and spontaneous hydrolysis. These chemical changes continue even after the blood sample

has been collected. Precautions must therefore be taken to ensure that initial levels remain unaltered (Jatlow 1988) using sodium fluoride or physostigmine, which can be added to plasma samples to prevent this rapid degradation. Without such precautions, metabolite levels will be artificially elevated while cocaine itself will not be detected.

Detection of benzoylecgonine in a urine sample is usually considered proof that the individual has used cocaine within the past 3 days (Weiss and Gawin 1988). Such a finding may have serious consequences for that individual. Employees typically receive warnings following an initial positive urine screen, and are also referred to an employee assistance program. Subsequent positive findings may result in loss of their jobs.

Individuals in treatment for drug abuse are sometimes discharged from the program if a positive test result is obtained more than 3 days after admission. Weiss and Gawin (1988) have identified several limitations to this strategy. The decision to employ the 3-day rule is based on short-term studies of research subjects who received relatively low drug doses for short periods. However, Weiss and Gawin found that cocaine's major metabolite, benzoylecgonine, can be detected for as long as 10 to 22 days after cocaine use in the urine of high-dose cocaine abusers. Clearly, discharge from a treatment program after three days because of a positive test result is unadvisable, since drug metabolites may be present long after a single high dose.

The positive identification of cocaine metabolites in body fluids provides no certain indication of performance impairment at the time of sampling or, for that matter, when the drug was used. Further studies documenting cocaine's acute and chronic effects on psychomotor performance correlated with blood levels of the drug are needed to assess the utility of such measures for indicating possible functional impairment.

Cardiovascular Toxicity

Data from DAWN indicate that there was a five-fold to six-fold increase in cocaine-related admissions to emergency rooms between 1984 and 1988. Cocaine-related deaths rose from 628 in 1984 to 2,163 in 1988. But even this number may be an underestimate. Mittleman and Wetli (1987) recently reanalyzed autopsy material from 24 patients who presumably suffered a sudden "natural" death; 11 of these patients were found to have cocaine in their blood.

Cocaine's toxic effects, which might account for such cases of lethality, appear to be directed at the heart and blood vessels, resulting in blockages of blood circulation (infarcts), abnormalities in the heart's rhythm (arrhythmias), and strokes. Heart stoppages (cardiac arrests) and generalized seizures are also frequently reported (Isner et al. 1986). Cocaine's cardiovascular effects are extremely complex because the drug has multiple actions on cardiac function, including local anesthetic effects and stimulant effects due to the inhibition of neuronal reuptake of neurotransmitters. Because of this complexity, it is essential that studies designed to elucidate the mechanism of cocaine's action be conducted utilizing a model that preserves all physiological and anatomical functions of the system. Such experiments can only be conducted in a conscious, intact animal whose central nervous system remains integrated with the cardiovascular system.

Wilkerson has conducted a number of experiments using the intact dog to provide a greater understanding of the cardiotoxic effects of cocaine. Cocaine-induced increases in blood pressure were potentiated when dogs were pretreated with yohimbine, a selective alpha$_2$-adrenergic antagonist (Wilkerson 1989). The increases in blood pressure were even greater when atropine was added to the preparation, but pretreatment with the ganglionic blocker hexamethonium actually reduced the pressor effects of cocaine (Wilkerson 1988). These data are extremely important in that they identify specific neuronal mechanisms that alter

cocaine's cardiotoxic effects—especially because the doses used in these studies are comparable to those abused by human subjects. Many drugs, including over-the-counter cold preparations, have anticholinergic (i.e., atropine-like) effects. Thus, it appears that the toxic effects of cocaine can be amplified by other, presumably harmless drugs.

The precise mechanism by which cocaine exerts its toxic effects in humans is not completely understood, however. A review of case reports indicates acute myocardial infarction is a significant risk, even in users who have no evidence of earlier coronary artery disease. The evidence for cocaine-induced arrhythmias is less compelling because other conditions, such as metabolic imbalances secondary to generalized seizures, may cause these cardiac irregularities (Jonsson et al. 1983). Fatal ventricular arrhythmias are also common when the heart's blood supply is impaired (myocardial infarcts), even when drug use is not involved. Although infarcts are common in cocaine overdoses, a direct causal relationship between the drug and these cardiac arrhythmias is unproven. Heart arrhythmias have not been noted following cocaine administration to healthy volunteers, although the doses in these controlled administrations have generally been low (Johanson and Fischman, in press).

Coronary ischemic syndromes (reduced blood supply to the heart muscle) have also been linked to cocaine use. However, none of the reports actually measured cocaine in the blood or urine of these patients, so this relationship is not definitive. Wilkerson (1988) has reported that peripheral arterial spasms are related to cocaine administration in dogs. These circulatory abnormalities probably account for most deaths resulting from cocaine-induced heart failure. About 20 cases of cocaine-associated myocardial infarct have been reported in the past 5 years (cf. Isner et al. 1986; Mathias 1986). The majority involved individuals who had preexisting coronary artery disease and/or other coronary risk factors (such as being a cigarette smoker). It is particularly striking, however, that this toxic effect was also found in relatively young individuals who had no evidence of earlier coronary artery disease (cf. Gradman 1988). The mechanism of such dramatic toxic effects in reasonably healthy individuals is still uncertain, but the most widely accepted hypothesis is that the blood supply blockage (infarct) results from acute cocaine-induced coronary spasms.

Cocaine-induced increases in blood pressure—the drug's hypertensive effect—can also affect the brain. Hemorrhage into the subarachnoid space (bleeding into the space between the brain and its surrounding outer membrane) after cocaine snorting was reported by Lichtenfeld and colleagues in 1984. Reports soon followed of blocked blood circulation to the brain (cerebral infarcts) after crack smoking (Golbe and Merkin 1986). In addition, there is a report of cerebral infarction in a newborn infant whose mother used cocaine 48 to 72 hours prior to delivery (Chasnoff et al. 1986). There are now about 12 reported case histories of cocaine-associated subarachnoid hemorrhage (cf. Lichtenfeld et al. 1984; Wojak and Flamm 1987; Schwartz and Cohen 1984). It is a possibility worth exploring that cocaine use is involved in similar cases in which no other cause is apparent.

In summary, despite the lack of concrete evidence linking cocaine to cardiovascular events in human subjects, there is a growing body of circumstantial evidence suggesting that cocaine may lead to myocardial infarcts and strokes. However, parametric studies conducted in animal models have clearly supported the contention that cocaine increases myocardial oxygen consumption and interferes with cardiac vasodilation. Understanding the precise nature of the toxic effects of cocaine on the heart would be invaluable in designing successful programs for treating cocaine overdoses.

Treatment for Cocaine Toxicity

Historically, the nonselective beta blocker, propranolol, has been the drug of choice to relieve cocaine-induced agitation (Rappolt et al. 1977). However, the involvement of coronary spasm in cocaine-induced myocardial ischemia and infarction

suggests that this strategy should be reevaluated. Combatting the hypertension with a nonselective drug may worsen the problem by leaving peripheral alpha stimulation unopposed. Combined alpha/beta blocking therapy or a beta$_1$-selective agent, such as labetalol, is now regarded as a much safer treatment for cocaine toxicity (Dusenberry et al. 1987). Drugs such as nitroglycerine or the calcium channel blockers are more likely to be of therapeutic benefit in cocaine-using patients who have signs of myocardial ischemia. Nitroglycerine, administered sublingually or intravenously, is useful (Gradman 1988). Calcium channel blockers, such as nifedipine and verapamil, are also effective in relieving coronary spasm. Results of animal studies are encouraging: pretreatment with another calcium channel blocking agent, nitrendipine, has been shown to raise the required lethal dose of cocaine in rats by four times (Nahas and Trouve 1985).

Behavioral Toxicity

Early data obtained from animal studies found that cocaine administration acts as a cue for cocaine-seeking behavior (de Wit and Stewart 1981), and clinical studies have now shown that cocaine use increases craving for the drug (Jaffe et al. 1989). This is in contrast to heroin, which makes its users feel satiated. The fact that cocaine use increases an individual's desire for additional cocaine is perhaps one of the more insidious toxic effects of the drug. In addition, subjects who received a 4-hr slow injection of cocaine experienced extreme increases in suspiciousness, sometimes to the point of paranoia (Sherer et al. 1988). The suspiciousness behavior patterns were not related to plasma cocaine levels, prior drug use, or psychiatric symptoms and history. Such changes in behavioral patterns coupled with a loss of control over one's desire for more cocaine characterize the behavioral toxicity of cocaine dependence and form a unique spectrum of drug effects.

The behavioral toxicity of cocaine with respect to acute alterations of psychomotor performance has not been adequately explored. One study by Foltin et al. (1988) did evaluate the effects of cocaine on a learning task known as serial acquisition. Cocaine doses of 48 and 96 mg, administered intranasally, did not affect performance on the learning task, as measured in several different ways.

Behavioral effects observed during withdrawal are also evidence of cocaine's toxicity. Using information gathered from interviews, Gawin and Kleber have suggested that the cocaine withdrawal syndrome is composed of a number of specific phases (Gawin and Kleber 1986; Gawin 1988). The first phase, called the "crash," is a kind of reactive depression lasting for several hours, followed by a period of hypersomnolence (increased sleep) that may last for a few days. This early phase is somewhat similar to an alcohol-induced hangover. The severity of this state seems to have little predictive relationship or relevance to the degree of withdrawal signs and symptoms the subject experiences in later phases (Brower and Paredes 1987; Kleber and Gawin 1987a).

The second phase (withdrawal) begins when the patient awakens from the extended sleep. An initial feeling of joyfulness (euthymia) is replaced by feelings of lethargy lasting 1 to 10 weeks, and loss of ability to experience pleasurable feelings (anhedonia). The drug abuser recalls his or her earlier cocaine-induced euphoria and intense pleasurable stimulation and experiences a renewed level of cocaine craving that was absent during the first phase. If the patient does not relapse to cocaine use during this period when craving is most intense, a third phase (extinction) may follow. It lasts indefinitely, while the patient struggles to break down or extinguish the associations between the cocaine "high" and the people, objects, or events (conditioned cues, such as one's drug supplier or injection paraphernalia) connected with it.

Strategies for Treating Cocaine Dependence

A variety of treatment services exists, including inpatient and outpatient services, group therapy, self-help groups, exercise and positive health promotion,

aftercare, contingency contracting, and family therapy. These types of programs are not specific to cocaine dependence but reflect the strategies currently practiced by most drug treatment centers. It is clear that no single program is effective in treating all cocaine abusers. (See the chapter on treatment research in this volume.) Rather, the emphasis has been on a multifaceted approach customizing treatment to meet the individual's needs. For example, Tennant and Berman (1988) have outlined a program that merges pharmacotherapy with education and counseling. This section focuses on several promising new medications as well as the use of conditioning and desensitization techniques.

Pharmacological Treatments

Although the neurophysiological bases for cocaine-seeking behavior and withdrawal are not completely understood, Dackis and Gold (1985) have hypothesized that depletion of the neurotransmitter dopamine in the central nervous system is involved in cocaine craving. This concept has been criticized by Kleber and Gawin (1987b), who suggest that chronic exposure to cocaine produces supersensitivity of dopaminergic autoreceptors (Gawin and Kleber 1986). While these are different neurophysiological mechanisms, their functional effect is the same: they both result in decreased levels of dopamine in the brain. Regardless of the precise mechanisms, neurotransmitters, most probably dopamine, seem to play a pivotal role in cocaine dependence.

In the absence of a drug that blocks cocaine's action—an effective cocaine antagonist—the search for a useful drug to treat cocaine dependence has been aimed at helping the patient initiate and maintain abstinence. Several drugs for achieving this aim have been studied in the past few years. They include lithium; chlorpromazine and haloperidol; antidepressants such as desipramine, imipramine, trazodone, and maprotiline; dopamine-like agents such as bromocriptine and amantadine; and central nervous system stimulants such as methylphenidate.

One of the most important findings to emerge from treatment research is that treatment may have to be individualized because the factors which influence cocaine abuse vary. For example, high doses of the stimulant methylphenidate can act as a cue for cocaine-taking behavior, so its usefulness as a pharmacotherapy may be limited (Gawin et al. 1985). However, cocaine users who have been diagnosed as having attention deficit disorder may, in fact, benefit from methylphenidate treatment (Khantzian et al. 1984).

Three double-blind studies have demonstrated that desipramine treatment significantly reduces cocaine use, symptom scores, and cocaine craving (Giannini et al. 1986; Gawin et al. 1989), and desipramine doses of 75 to 200 mg/day have reduced cocaine craving and use by methadone-maintained patients (Kosten et al. 1987b). Cocaine abusers frequently suffer from depression, so the success of the tricyclic antidepressant drug desipramine in treating cocaine dependence was not unexpected (Giannini et al. 1986; Gawin et al. 1985; O'Brien et al. 1988).

A recent study by Fischman and Foltin (1988) evaluated the effectiveness of desipramine on cocaine self-administration in nondepressed volunteers in a controlled environment. Baseline cocaine self-administration levels were obtained during an initial 2-week inpatient phase. Subjects then began taking desipramine and were discharged for 2 weeks. During this outpatient phase, patients visited the laboratory every day for tests to determine their plasma desipramine levels. Subjects were then readmitted to the clinical research ward; desipramine treatment was continued and cocaine self-administration assessed again. Subjects consistently self-administered the same amounts of cocaine they had taken during the baseline period. However, their subjective responses, such as heightened vigor and attention, were reduced after the cocaine injections that occurred during desipramine treatment. In addition, the subjects reported an increase in the generally undesirable effects of cocaine use, such as anger and anxiety. Finally, the subjects were asked to indicate how much

they "wanted cocaine at that moment." Their frequency of wanting cocaine was reduced from 100 percent during the baseline period to 40 percent during desipramine treatment. Although actual cocaine self-administration was not affected by the antidepressant drug, these results suggest that desipramine may alter the subjective response to cocaine and may even attenuate cocaine's reinforcing properties enough to allow alternative reinforcers, such as those stressed during psychotherapy sessions, to become significant.

Another antidepressant, imipramine, was shown to block cocaine-induced euphoria, but there was no placebo control with which to compare this effect (Rosecan and Klein 1986). Jones (1986) reported that the antidepressant trazodone, which is more selective for serotonin re-uptake, had little or no effect on the "high" induced by intravenous cocaine. Gawin (1986) reported that chlorpromazine or haloperidol, two major tranquilizers that block dopamine receptors, reduced cocaine-induced paranoia but failed to alter cocaine-induced euphoria. In fact, patients actually increased their binges, most likely because these medications eliminated the paranoia and dysphoria that often result from cocaine use while preserving the cocaine high. Thus, it appears that chronic treatment with dopamine receptor blockers may be ineffective in treating cocaine abuse.

The above-mentioned pharmacotherapies for cocaine abuse have been directed toward altering the ability of cocaine to act on the brain. Another strategy is to give patients drugs like amantadine and bromocriptine that mimic dopamine and therefore might block craving for cocaine. However, amantadine failed to block cocaine self-administration in baboons (Sannerud and Griffiths 1988), suggesting it might not be useful in reducing cocaine craving in humans. On the other hand, bromocriptine itself is self-administered by rhesus monkeys (Woolverton et al., 1984), suggesting that it may have some abuse potential in humans. This is despite the fact that the drug has a number of disturbing side effects, such as nausea, headache, and, occasionally, even psychotic symptoms.

In a study by Tennant and Sagherian (1987), both amantadine and bromocriptine in combination with tyrosine and tryptophan, resulted in decreased cocaine craving in outpatients. However, there was no placebo control, and the dropout rate of more than 70 percent suggests that the side effects the bromocriptine dose (2.5 to 7.5 mg daily) may have been too aversive for the subjects.

Giannini and colleagues (1987) treated 30 cocaine abusers over a 6-week period with bromocriptine. In a subsequent study (Giannini and Billett 1987), subjects scored better (i.e. lower) on a psychiatric rating scale after being given a combination of bromocriptine and desipramine than they did after being given bromocriptine alone. Although bromocriptine treatment was terminated after 30 days, the rating scale scores continued to plummet for an additional 60 days. However, these data only reflect the alterations in the patients' perceived severity of cocaine withdrawal and do not necessarily reflect a treatment success because cocaine intake was not evaluated in this study.

Dackis and colleagues (1987) have shown that a single dose of bromocriptine can effectively block conditioned cocaine craving. This double-blind, placebo-controlled study showed that bromocriptine may be effective in attenuating environmentally induced (conditioned cue) craving for cocaine. It remains to be seen whether this effect is useful in a clinical setting, given bromocriptine's side effects and possible abuse liability.

Data suggesting that the serotonergic system is involved in stimulant self-administration were reported in the Second Triennial Report. This area has continued to provide new and interesting findings for understanding abuse of central nervous system stimulants. Yu and colleagues (1986) demonstrated that a serotonin re-uptake inhibitor, fluoxetine, reduces amphetamine self-administration in rats when administered daily at a dose of 5 mg/kg. Reduced levels of amphetamine intake continued for 2 days after fluoxetine treatment was terminated, but this was most

likely due to the medication's persistence (long half life) in the animals' bodies.

One of the more important goals of treatment programs is to develop an effective way of reducing cocaine abuse in opiate-dependent individuals. Cocaine abuse among methadone maintenance clients is rapidly increasing (Kosten et al. 1987a). Because of this, and the added risk of spreading infectious diseases such as AIDS, a safe and effective treatment for both opioid and cocaine dependence would be invaluable in improving public health. Recent findings that buprenorphine (an opioid partial agonist that has been found useful in treating opiate dependence) reduces cocaine self-administration in humans (Kosten and Kleber 1988) and in monkeys (Mello et al. 1989) are very encouraging. The animal data (Mello et al. 1989) are especially important because buprenorphine was found to reduce cocaine intake by 91 to 97 percent without significantly reducing food intake, suggesting that buprenorphine's effectiveness is not due to nonspecific suppression.

A recent report of the results of structured interviews with a series of cocaine abusers found that 9 percent of the respondents had symptoms of eating disorders, such as anorexia nervosa and bulimia (Jonas et al. 1987). In sharp contrast, the reported rate of eating disorders among the general population is only 0.5 percent to 3 percent. However, it is unclear how cocaine's anorectic effects bear on these findings. The association of substance abuse with psychiatric disorders (see chapter on dual diagnosis in this volume), especially with depressive illness and eating disorders, suggests that treating abnormal behavioral patterns associated with these disorders may help prevent or ameliorate cocaine abuse.

Nonpharmacological Treatments

During the 2 to 10 weeks after a patient stops taking cocaine, conditioned cues may play an important role in precipitating cocaine craving and leading to a relapse to cocaine abuse (O'Brien et al. 1988; Gawin 1988). A conditioned cue can be any object, place, person, or event associated with the earlier cocaine high. Examples of such cues might include seeing one's former cocaine supplier, watching someone use cocaine, or being in a place or situation associated with cocaine use. Such cues precipitate cocaine craving because of their repeated association with cocaine use. This association can be extinguished if the cues are experienced in the absence of cocaine. O'Brien and colleagues (1988) have attempted to treat patients by specifically extinguishing the salience of the conditioned cues. Cues specific to the experience of the individual are presented in the absence of cocaine-induced euphoria so that the link between the conditioned cue and the cocaine-induced high is gradually weakened. Unfortunately, the success rate of such treatments has not been particularly high, suggesting that there may be variables controlling the subject's response to conditioned cues. As mentioned in the Pharmacological Treatments section in this chapter, psychiatric comorbidity must be considered in treating the cocaine abuser (Weiss and Mirin 1986; Gawin 1988). Weiss and Mirin (1986) identified five subtypes of cocaine abusers on the basis of clinical evaluation, family history data, and response to specific treatments. These subtypes are patients who may use cocaine to self-medicate depression by seeking euphoria; bipolar or cyclothymic disorders by modifying mood swings; attention deficit disorder; narcissism by enhancing social acceptance or bolstering self-esteem; and antisocial behavior by maintaining distance from society. Applying selective psychiatric diagnostic criteria to cocaine abusers may enable improved tailoring of treatment programs and medications to selected subpopulations.

Although many medications discussed above have been used to facilitate abstinence, there are no known medications that prevent relapse to cocaine abuse. This is an important distinction because a medication that alleviates withdrawal symptoms may not necessarily prevent relapse to cocaine abuse. Psychotherapeutic intervention is currently used to prevent relapse; however, because relapse rates are high, it may be wise to employ medications that reduce the craving

for cocaine or its effects in combination with psychotherapy.

Animal research has provided extremely useful information about cocaine's reinforcing properties and the conditions under which the drug is self-administered, which can be generalized to human subjects (Fischman 1988). As an example, environmental factors may play an important role in treatment. Schenk and colleagues (1987) housed rats either in isolation or in groups for 6 weeks. At the end of this period, the rats were tested for their development of intravenous cocaine self-administration behavior. The rats housed in groups failed to develop consistent patterns of cocaine self-administration, whereas the rats housed in isolation readily learned the procedure to receive cocaine injections. These data may provide some additional insight into factors affecting cocaine self-administration. They suggest that attention should be given to relevant environmental factors in developing more effective treatment programs for the cocaine-dependent patient. In addition, they may have direct implications for predicting and ultimately preventing cocaine abuse.

MDMA Abuse and Toxicity

The term "designer drug" is often associated with MDMA, known to drug abusers as "ecstasy" or "Adam," and other analogs of methamphetamine. By producing a drug that is chemically slightly different and therefore not legally restricted, its producers hope to avoid the legal penalties for distributing a controlled substance. In the case of MDMA, the parent drug is methamphetamine (i.e., "speed"), which was widely abused during the 1960s and is reportedly now undergoing a resurgence of use in the form of "ice."

The effects of MDMA have been described by users as resembling those of both cocaine and LSD. Shulgin and Nichols (1978) provided the first description of MDMA's subjective effects. They reported that it induced an altered state of consciousness and made patients receptive to psychotherapeutic intervention. The results of a number of uncontrolled studies suggested that MDMA facilitated communication and heightened empathy. This effect was interpreted as indicating that MDMA would be a useful adjunct to insight-oriented psychotherapy (Downing 1986; Greer and Tolbert 1986). As a result of growing concern over its abuse liability, MDMA and other analogs of controlled substances were included in Schedule I of the Controlled Substances Act under the Controlled Substance Analogue Enforcement Act, Anti-Drug Abuse Act of 1986 (Public Law 99-570).

MDMA's effectiveness as an adjunct in psychotherapy is supported only by anecdotal reports; there have been no double-blind, dose-response, controlled studies. Perhaps most important, MDMA has a demonstrated abuse liability both in humans (Peroutka 1987; Newmeyer 1986; Siegel 1986) and animals. For instance, Lamb and Griffiths (1987) have shown that baboons will self-administer MDMA.

In response to reports of widespread use of MDMA (U.S. Congress 1985), a number of laboratories began studies evaluating its potential neurotoxic effects. MDMA was subsequently found to cause long-lasting depletion of brain serotonin levels in rodents (Commins et al. 1987). Recent findings by O'Hearn and colleagues (1988) used immunocytochemical methods to view MDMA treated serotonergic axons, which they reported appeared swollen and fragmented. This provided the first concrete evidence that MDMA causes neurochemical deficits by inflicting structural damage to serotonergic axons. Recently, a number of laboratories have found that primates are four to eight times more sensitive than rats to the serotonin-depleting effects of MDMA (Ricaurte et al. 1988; Wilson et al., in press), and the dose-response curve was much steeper and therefore potentially more toxic in primates. To date, there are no controlled studies demonstrating the neurotoxic effects of MDMA in human subjects.

The significance of the neurotoxic profile of MDMA has recently been emphasized as a result of

reports of the neurotoxic effects of a structurally similar drug, fenfluramine (Kleven et al. 1988). Although the effects of fenfluramine on brain serotonin levels have been known for some time (Harvey and McMaster 1975), more recent reports have found fenfluramine to be three times more potent than MDMA in this regard. These new data, coupled with the previous reports, have precipitated a dilemma for the regulatory branch of the Food and Drug Administration because fenfluramine is an approved drug currently marketed in the United States as an appetite suppressant (its trade name is Pondimin). Proponents of MDMA's approval as a pharmacotherapy have emphasized that it is inconsistent to withhold MDMA from the market while fenfluramine continues to be listed in the *Physicians' Desk Reference*.

There are, however, a number of factors that must be considered when comparing MDMA and fenfluramine. As mentioned earlier, MDMA has significant abuse liability; it is self-administered by both animals and humans. However, neither monkeys (Woods and Tessel, 1974), nor baboons (Griffiths et al., 1978), will self-administer fenfluramine, and it has virtually no abuse liability for humans (Carabillo, 1978). Furthermore, rats appear to metabolize fenfluramine to norfenfluramine far more quickly and completely than humans who take the drug orally (Rowland and Carlton 1986). Since the half-life of norfenfluramine is roughly twice that of fenfluramine in rats, and because norfenfluramine appears to be at least as neurotoxic as its parent compound, this might account for the finding of significant toxicity in rats (Rowland and Carlton 1986).

MDMA has been associated with fatal and near fatal toxic reactions (Brown and Osterloh 1987; Dowling et al. 1987). Brown and Osterloh (1987) suggest that a hypersensitive reaction to MDMA is responsible for these toxic reactions. It would appear from the data presented by Verebey and colleagues (1988) that these observed toxic reactions were due instead to consumption of very high doses; MDMA plasma levels were 60 to 70 times (6.5 to 7.0 g/mL) those obtained after a standard (150 mg) dose of MDMA. In addition, they reported that in human subjects MDMA may be metabolized to MDA, a more potent neurotoxin than MDMA. In the report by Dowling and colleagues (1987), three of the patients had underlying cardiovascular or respiratory disease that may have enhanced the drug's toxicity.

OTHER ISSUES

Methamphetamine

Methamphetamine, like cocaine, is a psychomotor stimulant drug. It falls within the amphetamine family, a group of chemically related drugs that produce similar behavioral and physiological effects. These effects include euphoria, increased alertness, the perception of improved self-esteem and self-confidence, impaired judgment, and impulsiveness. Acute and chronic use of methamphetamine typically results in nervousness, irritability, restlessness, and insomnia. Amphetamine psychosis, a type of paranoia, can also result. These effects were extensively documented in the Second Triennial Report.

One major difference between cocaine and methamphetamine is duration of action. The half-life for cocaine's euphoric effects is less than 45 minutes, while that for methamphetamine is 3 to 6 hours (Ray and Ksir 1987). Therefore, one can expect that the period of stimulant-induced euphoria would be much longer in methamphetamine abusers and that likewise the period of impaired judgment will be longer.

Recent research evidence suggests that permanent neurological changes and deficits can result from chronic methamphetamine use. Laboratory research with animals has shown that chronic administration of methamphetamine results in neurotoxic effects on the brain, permanently affecting levels of the neurotransmitters serotonin and dopamine (Seiden and Ricaurte 1987). Other physiological effects such as increased body temperature and rapid respiratory and cardiac rates have been reported in many cases. Death

from acute overdose, which is rare, is usually preceded by an elevated body temperature, cardiovascular shock, and convulsions.

Since 1987, the smoking of crystals of very pure methamphetamine ("ice") has become a common method of taking the drug in Hawaii and on the West Coast and is now beginning to appear in the Midwest. As with cocaine, smoking methamphetamine compounds its effects and promotes rapid addiction. NIDA and other Federal agencies concerned with drug abuse and illicit drug distribution are monitoring the indicators of methamphetamine abuse through a variety of surveillance systems (Hall et al. 1988).

Look-Alike Drugs

In the Second Triennial Report, the issue of look-alike drugs was discussed, and a review of their history has recently been published (Morgan et al. 1987). Look-alikes are tablets or capsules manufactured to resemble legitimate pharmaceutical products and are frequently sold as appetite suppressants and antifatigue medication. They typically contain caffeine, ephedrine, and phenylpropanolamine, either alone or in combination. Morgan and colleagues (1987) point out that the look-alike market expanded substantially from 1977 until 1981. The Food and Drug Administration then declared the triple combination (caffeine, ephedrine, and phenylpropanolamine) a new drug, and thus were able to impose legal restrictions on the manufacture and distribution of these products. This action, along with well-planned raids of known manufacturers, significantly curtailed the distribution of these products. Additional legislation prevents the sale of combinations of two stimulants, so most over-the-counter diet products now contain only caffeine or phenylpropanolamine. An analysis of look-alike products suggests that their toxicity is not significant. Only nine published reports of toxicity related to look-alikes have appeared in the literature (cf. Morgan et al. 1987), indicating that these substances do not usually pose a serious physical threat.

Caffeine

Concern over the use of caffeine, one of the most widely used drugs in society, has escalated. Issues raised in previous reports focused on the caffeine withdrawal syndrome and its impact on continued caffeine use. More recently, caffeine's reinforcing properties have been more carefully analyzed. Griffiths and Woodson (1988b) conducted a double-blind study that quantified the reinforcing and subjective effects of caffeine. This is the first study demonstrating the positive reinforcing effects of caffeine alone: the drug was given in capsules and not as coffee or tea. Although the drug was administered under the same circumstances for each subject, there were differences in the reinforcing properties of caffeine for various individuals. Compared to placebo, caffeine produced increases in subjective ratings of arousal and contentedness, and decreased caffeine craving. Higher doses induced dysphoric, anxiety-like subjective effects. In a review of the animal and human literature, Griffiths and Woodson (1988a) concluded that the reinforcing effects of caffeine are markedly enhanced in individuals who are physically dependent upon the drug. They also pointed out that caffeine's reinforcing properties are not nearly as intense as such classic drugs of abuse as cocaine or pentobarbital.

SUMMARY

Since the last Triennial Report to Congress, research efforts have made major progress in a number of areas in cocaine and stimulant abuse. We now have a much better understanding of cocaine's toxic effects on the heart and other organs, so emergency treatment measures have been refined. Both pharmacological and nonpharmacological treatments have been successful in certain populations so that treatment can now be individualized to meet the specific needs of each patient. Of great importance is that these successes are intimately tied to success in slowing the spread of AIDS and HIV infection among drug abusers. Laboratory research using both animal and human

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subjects continues to provide the foundation for understanding the neurochemical, neurophysiological, and behavioral mechanisms of action of cocaine. Such information has become a valuable tool for testing current treatment and prevention interventions and will be crucial to the development of future programs.

In light of these successes, four issues identified in the Second Triennial Report as important research considerations continue to receive attention. Polydrug abuse, biological markers of abuse liability, alterations in expectancy of drug effects, and more effective treatment programs are all currently the focus of a number of research programs sponsored by NIDA. The results of such efforts are and remain the only means to obtain the factual information that is so necessary to combat cocaine abuse.

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MARIJUANA AND THE CANNABINOIDS

INTRODUCTION

In the Second Triennial Report, several areas relating to the health consequences of marijuana abuse were identified that needed further research. These subjects included determination of the effects of long-term moderate and heavy use of marijuana on mental, pulmonary, immune, and reproductive functions; behaviors such as classroom performance and driving; development during pregnancy; and the accumulation of cannabinoids in fat tissue. This chapter summarizes the progress that has been made in these and other areas and evaluates current research on the effects of marijuana on the brain.

EPIDEMIOLOGY

Marijuana is the most widely used illicit drug in the United States. The Second Triennial Report noted that use had significantly decreased. This trend has continued over the past 3 years. For instance, figure 1 shows the trends in lifetime, annual, and 30-day prevalence of marijuana use among senior high school students (Johnston et al. 1989).

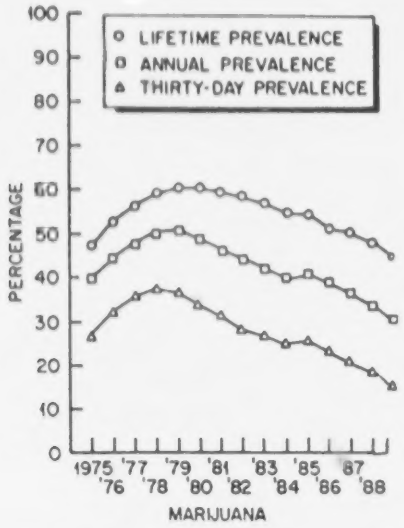

FIGURE 1. Trends in Lifetime, Annual, and 30-Day Prevalence of Marijuana Among All Seniors.

Changing perceptions of the harmfulness of marijuana use by high school seniors are equally important (Johnston et al. 1989). Table 1 indicates the dramatic change over the past decade in the proportions of high school seniors saying they perceive "great risk" of harming themselves if they "try marijuana once or twice," "smoke marijuana occasionally," or "smoke marijuana regularly." This continuing positive change is highly significant. Results from the 1989 survey of high school seniors indicate a continuing increase from 1987 in the proportion perceiving the drug as harmful.

Despite these encouraging findings, there are still disturbing problems. For instance, the concentration of delta-9-tetrahydrocannabinol (delta-9-THC), the principal psychoactive ingredient of marijuana, in street samples remains high and is again increasing (El Sohly and Abel 1988). Figure 2 shows that the average concentration of delta-9-THC in confiscated plant material peaked in 1984, fell in 1985 and 1986, but went back up in 1987 and 1988. It should be noted that the street material currently available is, on the average, three times more potent than that which was available in the early 1970s. In the past few years, there has been evidence of an "increasing sophistication on the part of growers in the ability to produce extremely potent material (approximately 15 percent of delta-9-THC)" (El Sohly and Abel 1988). Because the potency of street marijuana has so markedly increased, smaller amounts are needed to achieve the effects desired by the user. The stronger material may increase the likelihood of undesired adverse psychological effects (e.g., drug-induced anxiety or panic), particularly for the inexperienced user. However, the use of higher potency marijuana may also reduce the user's exposure to some of the smoke's harmful ingredients because the amount inhaled is also diminished. Thus the public health implications of consuming more potent material are uncertain. An additional public health concern is the increase in the number of confiscated samples containing the herbicide paraquat. Although the levels of paraquat that remain are not of immediate concern, this trend needs close monitoring.

HEALTH CONSEQUENCES

Tolerance and Dependence in Users

Our current understanding of marijuana tolerance and dependence was recently reviewed by Hollister (1986), who concluded that as with several other drugs relatively little tolerance develops to marijuana when doses are small or use is infrequent. Tolerance only becomes apparent after high doses and sustained, prolonged use. There have been relatively few reports of spontaneous withdrawal symptoms resulting from

TABLE 1. Trends in Perceived Harmfulness of Drugs

	PERCENTAGE SAYING "GREAT RISK"														
CLASS OF	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	'87-'88 Change
Q. How much do you think people risk harming themselves (physically or in other ways), if they . . .															
Try marijuana once or twice	15.1	11.4	9.5	8.1	9.4	10.0	13.0	11.5	12.7	14.7	14.8	15.1	18.4	19.0	+0.6
Smoke marijuana occasionally	18.1	15.0	12.4	13.4	13.5	14.7	19.1	18.3	20.6	22.6	24.5	25.0	30.4	31.7	+1.3
Smoke marijuana regularly	43.3	38.6	36.4	34.9	42.0	50.4	57.6	60.4	62.8	66.9	70.4	71.3	73.5	77.0	+3.5ss

the sudden interruption of chronic marijuana use. Previous studies conducted by Jones (1983) and others found that mild withdrawal symptoms appear in subjects who have received large doses of delta-9-THC for at least several days. However, only a small fraction of marijuana users consume this much drug, which probably explains the infrequency of withdrawal symptoms reported.

Very few animal or human studies in the past 3 years have examined dependence and tolerance. Given the large population of marijuana users and the infrequent reports of medical problems from stopping use, tolerance and dependence are not major issues at present. There are, however, good reasons for continued concern about the effects of marijuana on physical, mental, and social development, especially that of children and adolescents. Systematic clinical studies of the effects of standardized marijuana doses in this age group have not been conducted for obvious ethical reasons. Thus, it is not known whether dependence and tolerance are more or less likely to occur in this population. No carefully controlled clinical study has ever been reported, and the problem can probably never be adequately studied in this age group.

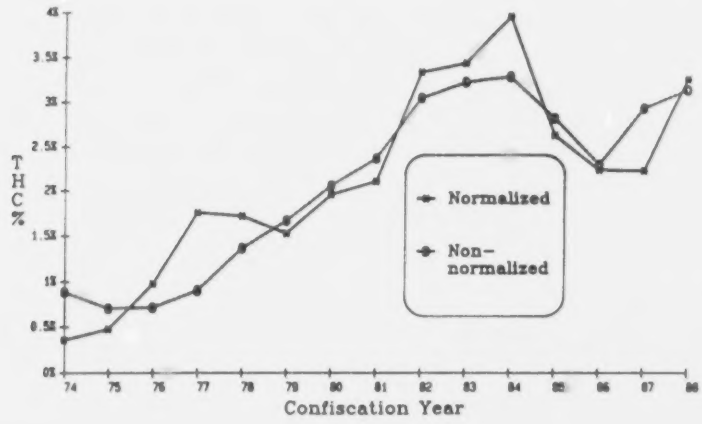

FIGURE 2. Normalized and Nonnormalized THC Percent by Year of Confiscation.

Treatment of Abusers

Although there are few reports of individuals' being incapacitated by abruptly stopping marijuana use, there are individuals who seek medical intervention because of their marijuana use. Roffman and Barnhart (1987) interviewed 225 people who responded to a public service announcement aimed at adult chronic marijuana abusers. Of these, 74 percent reported adverse consequences that they associated with the use of marijuana rather than with other drugs; 92 percent of those reporting such problems expressed an interest in being treated. Smith and colleagues (1988) used a combination of aversion therapy with cannabinoid-free marijuana and self-management therapy for 4 weeks to treat 22 volunteer chronic marijuana smokers, who significantly decreased their mean daily marijuana intake. The investigators concluded that this procedure has promise as a treatment program for chronic marijuana smokers. There are no reports evaluating the problems associated with discontinuing use among these volunteers. However, these studies indicate that there are some segments of the population that have difficulty controlling their cannabis use and seek professional assistance.

Effects on Fetal Development

There has been no dramatic increase in knowledge of how and to what extent marijuana affects fetal development. Studies in rhesus monkeys have demonstrated that delta-9-THC readily crosses the placenta and enters the fetus. THC administered early in pregnancy in female rhesus monkeys resulted in three out of five pregnancies being aborted after the drug injections began and a stillbirth at term in another animal. Daily THC injections during the middle or final period of gestation resulted in much less fetal loss (one premature birth and four live births when THC was given in the middle period; two premature births and three live births when the drug was given later in pregnancy (Asch and Smith 1986)). While animal findings like these are not directly translatable to humans, they provide additional evidence for the desirability of not using marijuana, particularly during pregnancy. In one study, however, the major metabolite of delta-9-THC, 11-nor-9-carboxy-delta-9-THC, did not readily cross the placenta and the fetus only poorly metabolized delta-9-THC (Slikker et al. 1988). In a study of human newborns from drug-dependent mothers (Ostrea et al. 1988), significant levels of delta-9-THC and 11-nor-9-carboxy-delta-9-THC were found in the meconium (i.e., the intestinal content of the full-term fetus), although these substances were undetectable in both maternal and fetal blood. This indicates that the meconium is a depository for cannabinoids in the fetus and that neither maternal nor fetal blood levels provide a true indication of fetal exposure over time. A study (Tyrey and Murphy 1988) of lactating (nursing) rats indicated that delta-9-THC inhibits suckling-induced prolactin release; delta-9-THC also affects oxytocin-induced milk ejection. These data represent "the first evidence that delta-9-THC inhibits neurohypophysial function during lactation" (Tyrey and Murphy 1988). When combined with earlier reports in prospective human studies (Gibson et al. 1983; Linn et al. 1983) linking smoking marijuana and an increased incidence of congenital abnormalities, these recent studies continue to indicate a need for increased research in this area. Walters and Carr (1988) treated pregnant rats with daily oral doses of delta-9-THC, delta-8-THC, and cannabidiol throughout gestation and lactation and found alterations in alpha-1-adrenergic and D2-dopamine receptors in the brains of their offspring. Perez-Reyes and Wall (1982) found delta-9-THC and its metabolites in the milk of two daily marijuana users who were nursing mothers and in the body fluids of their infants. The findings indicated that THC is concentrated in human milk and can be transmitted to the nursed infant. Although the effects on the infant of this form of chronic exposure are not known, their findings suggest nursing mothers should abstain from marijuana use.

Earlier animal studies have found pronounced effects of THC on reproductive hormones and on ovulation and spermatogenesis. However, clinical

studies in chronic human marijuana smokers have not consistently confirmed these. A study which appeared since the last Triennial Report suggests one explanation for these discrepancies is the development of tolerance to the drug's reproductive effects. Smith et al. (1984) found that administration of THC to 47 female rhesus monkeys initially disrupted their menstrual cycles, but that normal cycles were reestablished with chronic administration, probably because the animals became tolerant to the drug's effects. The authors concluded this is probably the result of an adaptation of neural mechanisms in the hypothalamus to the drug rather than of changes in the metabolism of THC.

Effects on the Immune System

In 1983, Munson and Fehr concluded that there was consistent evidence that cannabinoids produced defects in both cell-mediated and humoral immune systems of rats and mice, but no conclusive evidence that consumption of cannabinoids predisposed humans to immune dysfunction. Hollister (1988) recently reviewed the current status of research on cannabinoids and the immune system and concluded that this issue remains unsettled. The strongest support of any cannabinoid-induced immunosuppression is derived from in vitro studies where high concentrations of drug are required to produce any effect. Experimental studies most relevant to human use provide less compelling evidence for cannabinoid immunosuppression (Hollister 1988). However, the acquired immunodeficiency syndrome (AIDS) epidemic has raised new concerns regarding the immune system. Despite earlier conclusions that marijuana may have little or no effect on the normal immune system, new concerns are surfacing about the possible effects of drug abuse on an already compromised immune system. It remains to be determined whether cannabinoids play any role in individual susceptibility to AIDS or in the disease's progression.

Bronchopulmonary Effects

Because marijuana is deeply inhaled, the smoke retained in the lung longer than tobacco smoke, and because it contains many of the same toxic elements, there has been persistent concern about its possible effects on the respiratory system. Several more recent reports underscore the potential damage to pulmonary function that can result from chronic marijuana use. Tilles and others (1986) studied the effects of chronic marijuana smoking on gas exchange in the lungs of 15 healthy women who were daily marijuana users. They were compared with women who smoked cigarettes as well as a sample of nonsmoking women. Marijuana smoking with and without cigarette smoking significantly reduced gas exchange capacity.

Another study of 29 habitual daily marijuana smokers 25 to 45 years of age found that the marijuana smokers had a higher prevalence of abnormal airways than nonsmokers even when they did not also smoke tobacco cigarettes (Gong et al. 1987). In a related study, researchers from the same laboratory found an increase in abnormal cell yield using pulmonary lavage in marijuana smokers whether or not they also smoked tobacco (Barbers et al. 1987).

Behavioral Effects

Previous reports in this series have underscored marijuana's behavioral effects in such areas as learning, short-term memory, and skilled psychomotor performance. There is little question that marijuana use interferes with complex mental functioning as well as with skilled performance including driving (see below) or flying an airplane. Although less easily measured objectively, there is continuing concern by clinicians about the effects of regular marijuana use on the motivation and the emotional and psychosocial development of children and adolescents.

DETECTION OF MARIJUANA USE

There is still great controversy regarding constitutional rights of individuals required to have their biological fluids analyzed for the presence of abused substances. However, many private companies as well as governmental agencies remain committed to drug testing. There are two major reasons for these tests: to determine merely whether an individual has used an illegal drug and to determine whether drug use could have caused mental and physical impairment leading to injury or other dire consequences.

Although no new data have emerged regarding the metabolic profile of delta-9-THC in humans in the past few years, interest in the measurement of urinary metabolites for forensic purposes has increased (Agurell et al., in press). New methodologies can now detect urinary metabolites several days after the smoking of a single marijuana cigarette (Cook 1986). For example, by using the sensitive semiquantitative EMIT-d.a.u. immunoassay, Ellis and coworkers (1985) were able to measure urinary delta-9-THC metabolites in subjects up to 27 days after they had discontinued marijuana use. Agurell and colleagues (in press) have also improved detection methodology so that delta-9-THC in human plasma can now be measured at concentrations as low as 20 pg/mL. One of the factors contributing to the long half-life of delta-9-THC and its metabolites is the slow release of delta-9-THC from its storage in fat and its subsequent metabolism. It was not possible to quantitate low concentrations of delta-9-THC in human fat until recently, when Johansson and coworkers (1988) published a method that permits detecting less than 1 ng delta-9-THC/g in human fat.

Because much of the delta-9-THC in a marijuana cigarette is released into sidestream smoke, it is not surprising that the question of the effects of passive exposure to the drug has arisen. The increased sensitivity of cannabinoid assay detection techniques also makes it much more likely that trace quantities of cannabinoids will be detected in body fluids. Several studies have been conducted measuring cannabinoid levels in subjects who were passively exposed to marijuana smoke, often under unrealistic conditions. However, Mule et al. (1988) examined the urine of subjects who were passively exposed to marijuana smoke under more realistic circumstances. They were able to detect cannabinoids in urine, although the concentrations were quite low—less than 10 ng/mL. These low concentrations were below the typical range of 10 to 100 ng/mL found in occasional and moderate marijuana users.

Cone and others (1987) also conducted experiments to determine whether significant quantities of cannabinoids could be detected in body fluids after passive inhalation. Individuals were placed in a small, unventilated room where they breathed the smoke from 16 potent marijuana cigarettes. Blood concentrations of delta-9-THC as high as 18 ng/mL were measured, and significant quantities of marijuana metabolites were found in their urine. However, the authors concluded that most individuals would not normally choose to tolerate levels of smoke as noxious as those used in these experiments. Perez-Reyes and his associates (1983) measured cannabinoids in urine and plasma following passive inhalation under conditions more closely resembling those under which marijuana is likely to be smoked. They also found detectable levels although much lower than those detected in smokers. These findings indicate that passive inhalation can result in the presence of delta-9-THC in blood or discovery of the drug's metabolites in urine but is unlikely to produce the levels associated with actual smoking.

Another important issue is the relevance of the blood or urine concentrations of delta-9-THC and its metabolites to possibly impaired functioning. Even the courts must act without guidelines when determining what, if any, role marijuana plays in criminal cases in which delta-9-THC or its metabolites have been detected in the blood or urine of an accused person. Establishing a blood concentration of delta-9-THC or its metabolites that is likely to be associated with behavioral impairment in a way analogous to blood alcohol levels is difficult. The major problem is the

variability among subjects. Although there is also individual variability in alcohol sensitivity, there are more clearly defined limits of likely impairment.

Evidence continues to accumulate suggesting that marijuana used alone as well as in combination with other drugs plays a role in injuries and deaths. For example, examination of 500 consecutive post mortem urine specimens obtained by medical examiners in Maryland found that marijuana metabolites were common. The percentage of specimens containing cannabinoids in traffic-related deaths was lower than that found in other fatal accidents (6 versus 10 percent of the specimens). When used in combination, marijuana was most commonly used with alcohol (Isenschmid and Caplan 1988). A recent study of the presence of abused drugs in fatally injured drivers in Los Angeles County (Budd et al. 1989) found marijuana use (detected in 19 percent of samples) was only exceeded by that of alcohol (detected in 41.5 percent of the samples). A study of 317 of 359 randomly selected tractor-trailer drivers who were asked to participate voluntarily in a health survey (Lund et al. 1988) also found use of marijuana and other abused drugs was common. Cannabinoids were found in 15 percent of the drivers' blood or urine samples. The relationship between marijuana use and actual behavioral impairment in these individuals is, of course, uncertain since the levels detected cannot be clearly associated with diminished performance.

The past decade's research on the relationship between performance decrement and plasma delta-9-THC concentrations following marijuana smoking have been reviewed by Agurell and coworkers (in press). A few studies have shown a strong relationship between plasma concentrations of delta-9-THC and impairment in psychomotor performance. Most, however, have shown poor or no correlation. Agurell and colleagues (in press) conclude that a high correlation exists when group data are compared, but large individual differences in sensitivities probably explain the discrepancies in these experiments. With serial blood sampling, it nevertheless may be possible to predict the degree of intoxication or performance impairment. A single delta-9-THC blood level will not provide an adequately reliable prediction of intoxication. Despite these difficulties, it is essential that efforts be continued to establish a relationship between the quantity of cannabinoids in biological fluids and the degree of mental and physical impairment. Although this correlation will be extremely difficult to determine, the issue must be addressed if more meaningful conclusions from urine and blood testing are to be obtained. At present, it is possible to conclude only that an individual with positive findings has been exposed to marijuana at some time in the recent past.

The difficulty in establishing a relationship between blood concentrations of delta-9-THC and the degree of intoxication is further complicated by the reality that marijuana is frequently used with other drugs. One of the most frequently abused combinations is marijuana and ethanol. Perez-Reyes and coworkers (1988) recently demonstrated that driving skill decrements due to alcohol ingestion are significantly enhanced by marijuana; whereas alcohol appears to have relatively little effect on the marijuana "high."

THERAPEUTIC USEFULNESS

For millennia, cannabis has been reported to have a variety of therapeutic uses (Harris 1978), but until recently, the evidence was little more than anecdotal. With the advent of pure active principles and synthetic analogs, interest in possible clinical uses of the cannabinoids burgeoned. Reports have indicated that one or more of the cannabinoids have analgesic, anticonvulsant, antiglaucoma, antinauseant, and antiemetic effects. Only one of these therapeutic indications to date has been useful in practice. Nabilone, a synthetic cannabinoid, was marketed in Canada in 1981 as an antiemetic adjunct to cancer chemotherapy. The new drug gained little clinical acceptance. In 1987, delta-9-THC under the trade name Dronabinol was introduced in the United States as an antiemetic to control the nausea and vomiting accompanying cancer

chemotherapy when they are not relieved by the usual antinauseant drugs. Dronobinol has been well received by physicians in the United States, and there is little evidence that it is being abused.

In 1986, it was reported that cannabidiol (CBD), a nonpsychotropic cannabinoid found in the plant, reduced dystonia in five patients with movement disorders resulting from involuntary muscular contractions (Consroe et al. 1986). There was, however, an increase in parkinsonism-like signs and symptoms. This preliminary noncontrolled study, which was not double-blind (that is, the physician knew the patient was receiving the drug), prompted additional animal studies (Conti et al. 1988; Consroe et al. 1988) and another open-labeled clinical trial involving four patients with Huntington's chorea (Sandyk et al. 1988). Although there appeared to be improvement in some patients, these preliminary results need to be confirmed and extended in carefully controlled studies.

BASIC RESEARCH

Dependence in Animals

Determining the dependence liability of marijuana and its active principle, delta-9-THC, in animals has proven difficult. Most studies have been unable to demonstrate clear withdrawal signs and symptoms even after prolonged exposure to the drug (Dewey et al. 1972; Harris et al. 1974; McMillan et al. 1970; Stefanis et al. 1976). Self-administration studies in animals have generally failed to demonstrate reinforcing effects for the drug. Recently, Beardsley and colleagues (1986) reported a behavioral withdrawal syndrome after giving rhesus monkeys modest doses of delta-9-THC for 10 days. In these experiments, animals trained on a fixed-ratio (FR) reinforcement schedule for food received a slow, continuous intravenous infusion of the drug. Dosage used had little direct effect on rates of responding for food during the infusion; however, marked decreases in responding occurred during drug withdrawal. These effects began on day 2 of withdrawal and persisted for over a week. Results were replicated, and an additional experiment carried out at higher doses for a longer period. In the animals receiving this regimen, a marked reduction in response rate was observed by day 2 or 3 of withdrawal. When delta-9-THC was readministered to the monkeys, reversal of the withdrawal effects occurred. Administration of the narcotic antagonist naloxone failed to precipitate a withdrawal, indicating that the phenomenon observed was not opioid in nature. In most cases, this marked disruption of operant behavior occurred without any observable changes in overall behavior. When signs and symptoms did occur, they resembled those reported for humans and lasted for a similar amount of time (Jones and Benowitz 1978; Mendelson et al. 1984). Beardsley and colleagues indicate that such withdrawal effects suggest that more attention should be focused on the possible behavioral consequences of discontinuing cannabis use in humans. The researchers conclude that "The more subtle behavioral effects which we suggest may be produced by low doses may contribute to the maintenance of cannabis use, and warrant further investigation" (Beardsley et al. 1986).

Mechanism of Action

The rapid increase in the use of marijuana that occurred in the late 1960s and early 1970s resulted in an intensive research effort to identify the effects of cannabinoids on normal physiological function. There has been particular interest in the effects of cannabinoids on the brain in an effort to better understand their behavioral effects. Although much information has been gathered on the biochemistry of cannabinoids in the brain, it is unclear whether biochemical effects are responsible for the behavioral alterations caused by marijuana use. It is reasonable to ask why answers to this question have not been forthcoming. Part of the answer may be found by comparing cannabinoid research with that which has led to the much better understanding of opioid actions in the brain. Certainly opioids have been researched much more intensely for

a much longer period of time. Two major factors that led to the elucidation of the opioid receptors and the subsequent identification of the endogenous opioids were the availability of structural analogs with widely varying agonist potencies and specific antagonists. Although progress in cannabinoid research lags behind that of opioids, recent evidence suggests that these same tools are becoming available to cannabinoid researchers.

Considerable effort has been expended in synthesizing cannabinoid analogs largely because of the need to develop new therapeutic agents (Razdan 1986). These synthetic analogs have also been extensively used to characterize cannabinoid actions. An impressive array of central biochemical processes (neurotransmitters, enzymes, receptors, etc.) have been shown to be altered by natural cannabinoids as well as by synthetic analogs (Martin 1986; Dewey 1986). It has not been until the past few years, however, that attention has been focused on the use of potent cannabinoid analogs as molecular probes. Although it has been known for many years that dimethylheptylpyran (DMHP) exhibits very potent cannabinoid effects, it was not until recently that Mechoulam and colleagues (1987, 1988) synthesized 11-hydroxy-dimethylheptyl-delta-8-THC, a compound structurally related to DMHP. This analog also proved to be very potent, and its stereoisomers exhibited greater than hundredfold stereoselectivity in several animal behavioral tests (Mechoulam et al. 1987; Little et al., in press).

For the past several years, other synthetic analogs have been emerging that are both highly potent and highly stereoselective (Melvin and Johnson 1987; Little et al. 1988). It is these properties of the analogs which suggest very specific mechanisms in the central nervous system that are involved in the behavioral effects of the cannabinoids. Although previous attempts using radiolabeled delta-8-THC failed to clearly identify a cannabinoid receptor (Harris et al. 1978), the availability of these new potent analogs has generated a renewed interest in possible receptors. Nye and coworkers (1985) characterized a cannabinoid binding site by using a radiolabeled trimethylammonium (TMA) derivative of ^{3}H-delta-8-THC. Later, they isolated a substance from rat brain that has the characteristics of a myelin basic protein with a molecular mass of 14,500 daltons. This substance exerted a high affinity (4 nM) for the ^{3}H-5'-TMA-delta-8-THC binding site, prompting these investigators to suggest that there were endogenous ligands for this site (Nye et al. 1988). It does not appear, however, that this binding site is associated with psychoactivity, because nonpsychoactive analogs have a high affinity for it.

More recently, Devane and colleagues (1989) characterized a cannabinoid binding site in the brain by using the biologically active bicyclic cannabinoid analog CP 55,940. This analog exhibited high affinity (KD=133 pM) for the binding site, which was consistent with its pharmacological potency (Little et al. 1989). In addition, this site appeared to be associated with cannabinoid behavioral effects in that behaviorally active cannabinoids competed for binding, whereas behaviorally inactive analogs did not. In addition, Howlett and coworkers (1988) have shown that CP 55,940 and related cannabinoids are highly effective in inhibiting adenylate cyclase in neuroblastoma cell membranes and that their potencies correlate with their affinities for the CP 55,940 binding site in the rat brain.

Although it now appears that a cannabinoid receptor may exist, there are several research questions that need to be answered. First and foremost, what is the functional significance of this binding site? It may be a receptor that is responsible for the psychotropic effects of marijuana. An antagonist should be found that acts at this receptor. Although there have been numerous attempts to antagonize the pharmacological effects of cannabinoids by using many different drugs, these studies resulted in what is more likely a modulation of cannabinoid effects than an antagonism. There have been few studies devoted solely to synthesis and evaluation of cannabinoids for antagonistic activity. The failure to develop a specific antagonist of delta-9-THC raises the question of whether the tests that have been employed are appropriate for assaying the ac-

tivity of putative antagonists. Some evidence lends encouragement to the search for an antagonist. Beardsley and colleagues (1987) showed that delta-9-11-THC blocked the effects of delta-9-THC on conditioned responding in rhesus monkeys. In addition, Jorapur and coworkers (1985) showed that a nitrogen-containing analog of cannabidiol was able to partially block the antinociceptive properties of delta-9-THC in mice. Burstein and colleagues (1987) have also reported that 9-nor-9-carboxy-delta-9-THC is capable of blocking catalepsy induced by delta-9-THC in mice. This finding is intriguing and warrants further investigation. If it is ultimately proven that the major metabolite of delta-9-THC also serves to inhibit the actions of delta-9-THC, then considerable research effort will be needed to clarify this interaction, particularly given the prominence of delta-9-THC effects in the presence of this acid metabolite. All of these antagonism studies are far from conclusive, but they do point to some of the problems investigators face in attempting to develop an antagonist.

The neuropharmacological effects of cannabinoids have been investigated by several laboratories. Tripathi and coworkers (1987) demonstrated that the most consistent effect of cannabinoids, both psychotomimetic and non-psychotomimetic, was to increase acetylcholine levels and to decrease acetylcholine turnover in the hippocampus. They concluded that this cannabinoid effect on cholinergic mechanisms is probably more closely related to central nervous system depression than to a specific psychotomimetic activity. Taylor and colleagues (1988) microdialyzed the corpus striatum with delta-9-THC and found a twelvefold increase in the levels of dopamine without any alterations in dopamine metabolite levels. They concluded that infusion of delta-9-THC at this dose level increases the release of dopamine without altering neuronal uptake. Investigators have recently implicated other neurotransmitter systems in delta-9-THC actions. For example, Pertwee and Greentree (1988) examined the interaction of delta-9-THC and flurazepam and suggested that the gamma-aminobutyric acidnergic system may be involved in the behavioral effects of cannabinoids.

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PHENCYCLIDINE (PCP) AND RELATED SUBSTANCES

INTRODUCTION

For reasons that are not clear, phencyclidine (PCP) abuse is largely restricted to the United States, where it is particularly widespread in specific urban areas such as Washington, D.C., and among certain populations (Thombs 1989). Phencyclidine has a fascinating pharmacology, and recent developments in understanding its mechanism of action have produced renewed interest in this drug and others like it.

Phencyclidine was introduced into clinical medicine as an injectable anesthetic agent in the 1960s. It had a unique spectrum of anesthetic effects: it anesthetized humans without producing the cardiovascular or respiratory problems associated with most other anesthetic agents; considerable muscle tone was retained, and reflexes were not suppressed during anesthesia; and, in contrast to other

injectable anesthetics, phencyclidine produced analgesia in addition to anesthesia and amnesia. It was withdrawn from clinical use because, in a significant portion of the patient population, psychotomimetic effects occurred upon emergence from anesthesia. Ketamine, a phencyclidine analog with pharmacological properties nearly identical to phencyclidine but with a shorter duration of action, is still currently used as an anesthetic-analgesic in certain situations. The bizarre behaviors that have been observed both upon emergence from anesthesia and in phencyclidine abusers have led many to suggest that phencyclidine may be a useful model of schizophrenia (see, for example, Balster 1987).

MECHANISMS OF ACTION

Many of the behavioral effects of phencyclidine appear to be related to one of two neuronal mechanisms: it is a noncompetitive inhibitor of specific excitatory neurotransmission, and it interacts with neurotransmitter systems, e.g., dopamine. The former mechanism is probably responsible for the majority of phencyclidine actions, and is better understood at the present time than the latter. It will be discussed here in some detail.

Effects Related to NMDA Antagonism

Glutamate is an excitatory amino acid, present throughout the body, and acting as a neurotransmitter, communicating electrical activity from one neuron to another, in certain parts of the nervous system. Perhaps because glutamate is so ubiquitous, selective action of this compound may be attained through its interactions with several differentially sensitive glutamate receptors. One of these receptors is referred to as the NMDA receptor because it has been shown to be activated more than other glutamate receptors by the amino acid, N-methyl-D-aspartate. Stimulation of NMDA receptors by application of glutamate or NMDA opens ion channels and allows sodium and calcium to pass through the cell membrane; this change in the charge of the inside of the cell, relative to the outside, leads to a depolarization of the membrane. If the depolarization is sufficiently large, the neuron will "fire," and pass the electrical charge along its membrane and release neurotransmitters to the neurons to which it is adjacent.

The phencyclidine recognition site is located within the ion channels in the neuronal membrane that are opened by application of glutamate or NMDA (figure 1). Phencyclidine and other drugs that bind to the phencyclidine site restrict movement of the ions through the channel and thus act to reduce the effect of glutamate and therefore to reduce the activity of the neuron. Thus, the actions of phencyclidine-like drugs are in opposition to those of glutamate at its NMDA binding site. Since the opposition is not caused by affinity at the same site, phencyclidine and other drugs that bind at the phencyclidine site are referred to as *noncompetitive* antagonists of NMDA. A large number of other drugs bind to this phencyclidine binding site including ketamine, (+) SKF 10,047, dexoxadrol, metaphit, and MK-801 (figure 1).

Although considerable effort has been made to synthesize an antagonist of phencyclidine, to date there has been little progress toward that goal. In some other drug-receptor systems, the benzodiazepines, for example, once binding sites were clearly identified, it was a simple matter to identify drugs that bound to the site, and test each of them for behavioral effects. Drugs that bound to the site but had little intrinsic action were prime candidates as pharmacological antagonists. Although there has been speculation that certain compounds, metaphit, for example, might be effective antagonists (e.g., Contreras et al. 1985) (metaphit binds very tightly to the receptor and cannot be washed out, a property that has been linked to receptor antagonism in other drug systems), further analysis has revealed that these drugs have primarily phencyclidine-like effects rather than having phencyclidine antagonist effects (Koek et al. 1987; Beardsley and Balster 1988). In some sense, it would appear unlikely that an antagonist to phencyclidine can

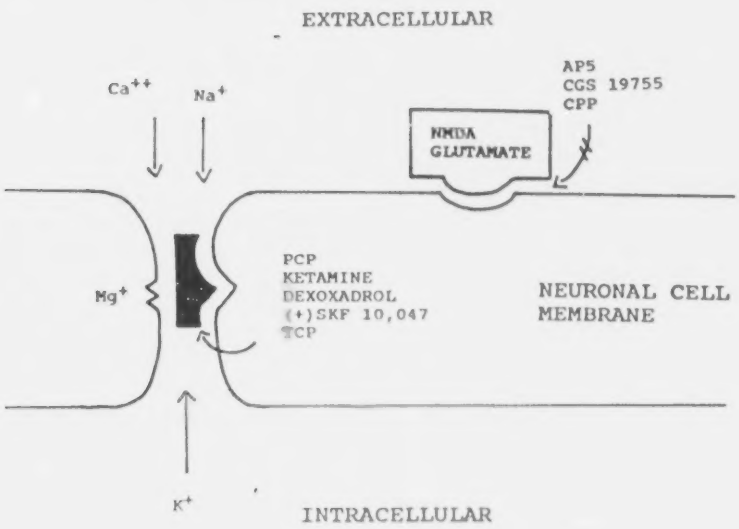

FIGURE 1. Schematic Diagram of the MNDA Receptor Complex and Compounds That Act as Competitive (AP5, CGS 19755, CPP) or Noncompetitive (PCP, Ketamine, Dexoxadrol (+) SKF 10,047, TCP, MK-801) Antagonists of NMDA.

be developed. Since binding to the phencyclidine binding site apparently produces a physical barrier to ion flow, any drug that bound to this site might be expected to have this effect. Thus, while a phencyclidine antagonist is of sufficient interest and scientific use that the search for it should continue, those involved in this search should be aware of the difficulties and frustrations that may lie ahead.

There are other drugs that act as *competitive* antagonists of NMDA. These drugs act to block the effects of glutamate by attaching directly to the NMDA receptor site. If the effects of uncompetitive NMDA antagonists, such as phencyclidine, are similar to those of competitive NMDA antagonists, such as AP5 or CGS 19755 (figure 1), it would be further demonstration that phencyclidine's effects are mediated through reduction of glutamate action on NMDA receptors. Most competitive NMDA antagonists do not readily cross the blood-brain barrier and thus are difficult to evaluate in behavioral experiments. Where comparisons have been made, similarities are sometimes encountered, and differences are also frequently observed. These will be noted as appropriate in the discussion of the behavioral effects of phencyclidine given in this chapter.

Effects Related to Dopamine

Phencyclidine has some effects such as locomotor stimulation and stereotypy, that appear to be related to increased release or decreased inactivation of dopamine in the central nervous system. This effect does not appear to be mediated through NMDA receptors (e.g., Wood and Rao 1989; French et al. 1987; Snell et al. 1988). Some chemical analogues of phencyclidine have been shown to have strong inhibitory effects on dopamine reuptake through mechanisms that appear similar to those associated with cocaine's action (Zimanyi et al. 1989; Vignon et al. 1988). Nevertheless, NMDA itself has been shown to produce large increases in dopamine in certain areas of the central nervous system, an effect that was blocked by administration of phencyclidine (Carter et al. 1988). Thus, the relationship between phencyclidine, the NMDA receptor system, and dopamine is not yet completely understood, and further research is necessary to identify more precisely how these systems interact.

TOLERANCE

Tolerance occurs as a function of chronic administration of a drug. It has been variously defined as: a reduced capacity of a dose of a drug to produce a given effect; the need to increase the dose of a drug in order to recapture an effect obtained earlier by a smaller dose of that drug; and, in pharmacologically more precise language, as a shift to the right in the dose-effect curve produced by a drug. Tolerance to phencyclidine has been evaluated using a number of procedures, a variety of dosing schedules, and several different animal species. The results of these studies, not surprisingly, provide a rather cloudy picture of the nature and degree of tolerance to phencyclidine. It seems clear that tolerance does not develop uniformly to all the effects of phencyclidine. The drug has a number of behavioral effects in rodents, some of which appear to be stimulatory, e.g., increased locomotion, stereotypy, sniffing, and rates of some types of operant behavior. Other behaviors suggest more of a depressant effect of phencyclidine, e.g., ataxia, and decreased rates of operant behavior under some types of schedule conditions. Many of the experiments on the effects of chronic administration of phencyclidine suggest that there is tolerance to the depressant effects of the drug, but less tolerance and perhaps increased sensitivity to the stimulant effects of the drug (Leccese et al. 1986; Flint and Ho 1980; Nabeshima et al. 1987; Matsuzaki and Dowling 1985; French 1988). In spite of several exceptions (e.g., Wenger 1983), one generalization that seems rather safe to make is that the amount of tolerance development in any case is fairly small, less than a five-fold shift in the phencyclidine dose-effect curve (e.g., Balster and Woolverton 1981; Wenger 1983). In some instances, tolerance appears to be due to increased rates of drug metabolism, i.e., metabolic tolerance (Flint and Ho 1980, Freeman et al. 1984).

PHYSIOLOGICAL DEPENDENCE

Physiological dependence, as defined by the development of time-limited, drug-reversible withdrawal signs following termination of chronic drug administration, develops with phencyclidine. These signs, in the rhesus monkey, following 20-30 days of unlimited access to intravenous, self-administered phencyclidine and profound intoxication (4-7 mg/kg/day), included tremor, piloerection, penile erection, diarrhea, persistent vocalization, hyperresponsiveness, abnormal eye movements, teeth grinding, and ear and facial twitches. The peak of withdrawal was 12 to 16 hours following replacement of phencyclidine by saline, and the symptoms gradually decreased over a 36 hour period. Administration of 0.25 mg/kg phencyclidine completely abolished the withdrawal signs. Phencyclidine dependence does not depend on opiate receptor activity, since administration of naloxone, the opioid antagonist, did not precipitate these signs (Balster and Woolverton 1980).

In rats, following continuous intravenous infusion of 45 mg/kg/day phencyclidine for 7 days, withdrawal signs included slight body weight loss, piloerection, increased sensitivity to audiogenic seizures, and decreased exploratory behavior (Spain and Klingman 1985). Increased chewing and licking, facial twitches, and occasional seizures were observed in rats following termination of three-times-daily injections of 24 to 72 mg/kg/day phencyclidine for 2 weeks (Stafford et al. 1983).

Using disruption of food-reinforced behavior, a sensitive measuring technique, physiological dependence on phencyclidine has been reported with low chronic doses of drug. Slifer et al. (1984) reported disruption in food-maintained responding in monkeys eight hours after a continuous, 10-day, intravenous infusion of 1.2 mg/kg/day phencyclidine was stopped. Responding could be reinstated by administration of phencyclidine. Carroll (1987) found a similar disruption in food-maintained behavior in rhesus monkeys that had been given access to oral phencyclidine for 19.5 hours daily for 10 days, and drank between 5 and 50 mg/kg/day, depending on the concentration of drug and the individual animal. In both studies, behavior was disrupted for one to seven days. Withdrawal of higher doses of continuously infused phencyclidine

(12 mg/kg/day for 10 days) has been shown to suppress food-maintained responding in the rat without producing any grossly observable signs (Beardsley and Balster 1987).

Cross-dependence, whereby one drug is able to attenuate withdrawal signs produced by another drug, has been demonstrated between ketamine and phencyclidine (Beardsley and Balster 1987) and between (+) SKF-10,047 [but not (-) SKF-10,047] and phencyclidine (Stafford et al. 1983; Carroll 1987b). Cross-dependence is one indicator that drugs might be acting through similar pharmacological mechanisms.

There have been no clear reports in humans of withdrawal signs attributed to phencyclidine. Tennant et al. (1981) noted anecdotally that phencyclidine abusers report craving, lack of energy, depression, and physical discomfort when they discontinue phencyclidine use, and these feelings are in some way responsible for difficulty in continued phencyclidine abstinence. Burns and Lerner (1981), however, found no evidence of withdrawal signs in their review of the literature on chronic phencyclidine use in humans.

In summary, chronic administration of relatively large doses of phencyclidine, followed by termination of phencyclidine administration, results in a characteristic behavioral syndrome in monkeys and rats. Phencyclidine withdrawal signs are different from opioid or ethanol withdrawal signs, and might be less severe than opioid or ethanol withdrawal signs, although careful quantification and comparisons among drug classes is difficult. It is not clear, from either the studies in monkeys and rats, or the reports in humans, whether dependence on phencyclidine supports continued self-administration of the drug. It is generally thought that human opioid abusers deprived of their opioid and demonstrating opioid withdrawal signs, show increased tendency to locate, purchase, and administer the drug. How phencyclidine withdrawal affects phencyclidine-maintained behavior in animals or in humans has not been assessed to date.

SELF-ADMINISTRATION

Drugs that have been shown to have reinforcing effects in animals models are, with a few interesting exceptions, drugs that are abused by humans. Thus, animal preparations that can report the reinforcing effects of drugs are useful in predicting the abuse liability of these drugs, and in studying some of the procedures that might modify drug self-administration. One of the most frequently used and useful animal model of drug self-administration is based on animals, typically rhesus monkeys but also baboons, dogs, or rats, with an indwelling intravenous catheter, trained to respond on an available lever and receive intravenous infusions of various drugs and vehicles. A very wide variety of drugs have been studied using intravenous self-administration procedures, including central stimulants such as cocaine and amphetamine, depressants such as barbiturates, ethanol, and benzodiazepines, opioids such as morphine and heroin, and dissociative anesthetics such as phencyclidine and ketamine.

The reinforcing effects of phencyclidine via the intravenous route has been clearly demonstrated under a variety of conditions and in a number of different species (see Marquis and Moreton 1987). Monkeys (Winger et al. 1989), baboons (Lukas et al. 1984), rats (Marquis et al. 1989), and dogs (Vaupel et al. 1986) have all shown rates of phencyclidine-maintained responding that are higher than rates maintained by saline, indicating the reinforcing effects of this drug. When access to phencyclidine is relatively unlimited, monkeys will self administer sufficient drug to produce physiological dependence, as evidenced by the appearance of withdrawal signs when saline is substituted for phencyclidine (Balster and Woolverton 1980).

Other drugs that bind to the phencyclidine site, including ketamine (e.g., Moreton et al. 1977), (+) SKF 10,047 (e.g., Vaupel et al. 1986), dexoxadrol (Jacobson et al.,1987; Slifer et al. 1986), and (+) cyclazocine (Slifer and Balster 1983), have also been shown to maintain behavior at greater than saline-

maintained rates. MK-801 is less effective than phencyclidine in this regard, although it does maintain rates of responding above those maintained by saline (Koek et al.,1988; Winger et al. 1989). MK-801 has a slower onset of action in some conditions; if this is true when the drug is delivered intravenously, it may account for the lower rates of behavior maintained by this drug. The reinforcing effects of drugs appear to be enhanced when the drugs have a rapid onset of action.

CGS-19755, a competitive antagonist of NMDA, does not maintain self-administration behavior when it is available for intravenous delivery to rhesus monkeys experienced with ketamine-maintained behavior (Winger and Woods, unpublished observations). This negative result is complicated by the fact that CGS-19755 has a slow onset of action, which may account in part, or entirely, for the lack of reinforcing effects observed with this drug.

Phencyclidine is unusual in that its ability to maintain responding when it is available by the oral route has been quite thoroughly evaluated. Drs. Carroll and Meisch developed a procedure in which food-deprived rhesus monkeys drink large amounts of fluid in the presence of their daily ration of food. After experience drinking fluids that contain psychoactive drugs such as ethanol, barbiturates, or phencyclidine, the animals demonstrate the reinforcing effects of these drugs in that they consume them in preference to water and when food is not concurrently available. Sufficient oral phencyclidine self-administration occurred under these conditions to produce both tolerance (Carroll 1982) and, with long daily periods of phencyclidine availability, physiological dependence (Carroll 1987a). Phencyclidine analogues PCE and TCP also maintained behavior when they were substituted for phencyclidine under conditions of oral availability (Carroll 1982), and (+) but not (-) or (±) SKF-10,047 effectively maintained behavior when it replaced phencyclidine in the available fluid (Carroll 1987b).

DRUG DISCRIMINATION

There have probably been more reports of the effects of phencyclidine as a discriminative stimulus in animals than of any other behavioral effect of this drug and drugs like it. Fortunately, there is considerable agreement among these studies, so that a brief review should suffice to convey the general conclusions about drug discrimination studies. The procedure of drug discrimination involves training an animal subject to make one of two response (usually to obtain food) if it has been given a specific drug, and to make the other response if it has not been given drug. The drug in this situation thus becomes a discriminative stimulus, signalling which of the two responses is appropriate. Trained subjects can be given another drug, and they will indicate whether that drug has stimulus properties in common with, or distinct from, the drug to which they were trained.

It is generally thought that the stimulus properties of drugs in animals may reflect the subjective effects of drugs in humans who can also discriminate classes of drugs on the basis of their common stimulus properties. Thus, a drug that is shown to have discriminative similarity to phencyclidine in animal subjects may be presumed to have a similar set of subjective effects as phencyclidine in humans.

The generalizations that can be made about the discriminative stimulus property of phencyclidine are 1) that it can be trained in a variety of different animal species including rats (e.g., Cone 1984), mice (e.g., Middaugh et al. 1988), pigeons (e.g., McMillan et al. 1982), squirrel monkeys (e.g., Holtzman 1982), and rhesus monkeys (e.g., Solomon et al. 1982); 2) that other drugs that bind to the phencyclidine binding site including ketamine (Leander 1982); (+) SKF 10,047 (e.g., Slifer and Dykstra 1987), MK-801 (Koek et al. 1988 in monkeys; Willetts and Balster 1988 in rats); dexoxadrol (e.g., Jacobson et al. 1987; Slifer and Balster 1984-85), (+)-alpha-cyclazocine (Slifer and Balster 1988), metaphit in pigeons, but not rhesus monkeys (Koek et al. 1987), and a wide variety of phencyclidine analogues (Cone et al. 1984) are also

discriminated as being like phencyclidine; and 3) that the relative potency of these drugs in producing phencyclidine-like discriminative effects is similar to their relative potency at the phencyclidine binding site (e.g., Shannon 1981), suggesting a functional significance of this site. There is evidence that CGS-19755, a competitive antagonist of NMDA, does not have stimulus properties in common with ketamine (France et al. 1989). Whereas this may indicate that drugs that act at the phencyclidine binding site do not produce their discriminative stimulus effects by NMDA-receptor antagonism, more thorough studies of the pharmacodynamics of the current competitive NMDA antagonists, as well as tests with competitive NMDA antagonists that are more bioavailable, as they become available, will be necessary before any firm conclusions can be made.

LEARNING AND MEMORY

Studies in animals strongly support the notion that phencyclidine, and the substances like it that have been tested, can interfere with the acquisition and/or retention of learned information. It is to these studies we must refer when we are looking for correlates of the human experience of phencyclidine or ketamine-induced amnesia, e.g., when these drugs are used as anesthetics, and from the anecdotal reports of amnesia experienced by phencyclidine abusers.

It has always been fairly difficult, in animal studies, to separate the performance-disrupting effects of a drug from the drug's capacity to actually alter learning and remembering. One way these two have been studied independently is in a paradigm called "a repeated acquisition task." In this paradigm, animal subjects learn to respond on a series of levers in a specific order in the presence of a distinctive stimulus light. Once this order has been well learned, over a period of several weeks of daily testing, a different stimulus light is presented. In presence of this new stimulus light, the subjects must learn a new sequence of lever presses. After a specified period of time, the former stimulus light is reilluminated, and the subjects can earn food by responding in the order they learned originally. The subjects have several opportunities to learn the new task in the presence of the new stimulus, and the old stimulus, associated with the previously learned task is interspersed among the learning opportunities. The new task changes with every daily session; the old task remains the same. In this situation, the effects of drugs on learning—acquisition of the new task—can be contrasted to the effects of performance—rates of responding and errors made on the old task—at the same time.

The effects of phencyclidine and several phencyclidine-like drugs have been evaluated in repeated acquisition tests. In general, phencyclidine produces a relatively greater disruption in the acquisition component of the task than in the performance component of the task. This is less true with a number of other drugs that have been tested, including opioids (Moerschbaecher et al. 1985) and amphetamines (Thompson and Moerschbaecher 1984).

Other tests of learning and memory in animal subjects have also indicated that phencyclidine has a deleterious effect on learning and recall. Studies in rats suggest that long-term storage of information is disrupted when phencyclidine is administered (Handelmann et al. 1987), and that phencyclidine produces a retrograde amnesia for events learned immediately prior to drug administration (Nabeshima et al. 1986).

The phenomenon of long-term potentiation, whereby the shape of neuronal action potential is altered as a function of stimulation of the nerve, is thought by some to be the neuronal basis for learning and memory. There are data indicating that the NMDA receptor is uniquely involved in the development of long-term potentiation (Kauer et al. 1988). Thus, the effects of phencyclidine on acquisition and recall of information may eventually be understood at a more molecular level.

ANALGESIA

Ketamine, an analogue of phencyclidine with affinity for the phencyclidine binding site, enjoys use as an anesthetic-analgesic in clinical medicine in this country and throughout the world for the treatment of patients with extensive burns. Profound analgesia at close to anesthetic doses is obtained with ketamine, allowing for cleaning and redressing of these wounds.

There is a controversy in the animal literature about whether the analgesic effects of phencyclidine and phencyclidine-like drugs are through an opioid mechanism. If this were the case, these effects should be reversed by administration of an opioid antagonist such as naloxone. Several investigators have reported this to be the case (e.g., Smith et al. 1988); several more have refuted this claim in both animals and man (e.g. France et al. 1989; Maurset et al. 1989). In the rhesus monkey, phencyclidine and a number of phencyclidine-related compounds produced an increase in the latency with which the animals removed their tails from a thermos of warm water (France et al. 1989). A very similar effect was produced by opioid drugs. However, the effects of the opioids but not the phencyclidine compounds were antagonized by prior administration of the opioid antagonist quadazocine, indicating that the mechanism of analgesia was different for the two drug classes. Furthermore, the potency of phencyclidine in producing analgesia was strongly related to its capacity to produce anesthesia; opioids do not produce anesthesia, indicating that the two drugs are not related in their capacity to reduce the reaction to painful stimuli. Unpublished observations suggest that CGS-19755, which acts directly at the NMDA receptor site to block the effects of glutamate (figure 1) is also an analgesic, indicating that the mechanism by which phencyclidine produces analgesia is most likely via is uncompetitive inhibition of the excitatory amino acid neurotransmitter, glutamate, at its NMDA receptor site. This may also mean that CGS-19755 can serve as a new analgesic without the abuse liability of phencyclidine or ketamine.

CGS-19755 was described earlier in this chapter because it does not have stimulus properties in common with ketamine and phencyclidine. Therefore, it is not likely that CGS-19755 has the same subjective effects in humans as do these two drugs of abuse. Although CGS-19755 may not be useful as an anesthetic because of the very slow onset of its anesthetic effects, it is the profile of low abuse liability that scientists look for in the development of new anesthetics. Hence, both behavioral and pharmacological research are required to determine the utility and safety of new drugs.

IN UTERO EFFECTS

It is difficult to study the effects of maternal phencyclidine intake on human neonates because women seldom take phencyclidine as their only drug of abuse. Thus, any abnormalities in the infants could be due to the effects of cigarette or marijuana smoking, ethanol, cocaine, or opioid use, or a combination of use of these drugs. Also, as with any human study, it is difficult to be certain of the amounts taken of any of these drugs, or the time during gestation when drug administration occurred. In studies of pregnant women who denied use of drugs other than phencyclidine, there was no consistent pattern or abnormal morphology observed in their offspring (Wachsman et al. 1989). A larger than expected percent of the infants were small for gestational age, and although many of the children made up for this size deficit by the time they were one year of age, many others remained small. Fifty five percent of the infants born to women who used only phencyclidine showed a classic neonatal opioid withdrawal syndrome, compared with 83 percent of the infants of women who used both phencyclidine and opioids. The authors suggested that this syndrome may occur in neonates exposed to intrauterine drugs in general, rather than being specific to opioid-exposed fetuses.

Golden et al. (1984) found that, in women taking a number of drugs (none used opioids), phencyclidine

use alone accounted for a significant portion of the variance associated with the number of abnormalities in the neonates. The number of abnormalities was slightly, but significantly, larger than the number in a control sample, and were abnormalities of neurology and behavior (poor attention, slow reflexes) rather than of morphology. Differences in birth weight and size were not reported.

Studies in rodents, in which gestational time of drug administration, as well as the nature and dose of the drug, can be controlled also suggest that development of reflexes may be delayed in neonates exposed to phencyclidine in utero (Nicholas and Schreiber 1983). Phencyclidine also produces decreases in maternal weight (also reported by Hutchings et al. 1984) and in the body weight and length of the offspring (Nabeshima et al. 1987).

It appears at this time that there is no clear phencyclidine-induced complex of neonatal abnormalities. Offspring of mothers who have received phencyclidine tend to be smaller than offspring of normal mothers, and some may have slight neurological deficits. These effects are not large, and phencyclidine does not appear to warrant major concern as a teratogen.

TOXICITY

There are two aspects to phencyclidine intoxication that have warranted particular attention by the general public, as well as by law-enforcement and clinical personnel. Both aspects concern the relationship between phencyclidine abuse and aggressive behavior. There are reports of increased aggressiveness and "super-human" strength that develop in some people who take phencyclidine. Recent studies, including those of men arrested for criminal activity in Washington D.C. and New York City (Wish 1986) and evaluations of published clinical reports of phencyclidine intoxication (Brecher et al. 1988), indicate that if phencyclidine induces violent, criminal behavior, it does so only extremely infrequently. Although Wish (1986) noted that most men who had urines positive for phencyclidine were younger than those who had taken no drugs or other drugs, their crimes were more likely to be less aggressive than the crimes of those who had not taken phencyclidine. Khajawall et al. (1982) found no difference in the behavior of clients admitted for phencyclidine detoxification and those admitted for opioid detoxification. Thus, phencyclidine-induced aggression appears to be a rare phenomenon, if it occurs at all.

The second interesting aspect of phencyclidine intoxication is that episodes of psychosis have been reported in a small percentage of people taking or receiving phencyclidine. These psychoses may have combativeness and assaultiveness as symptoms. Although there appears to be more validity to reports of phencyclidine-induced psychoses than to the reports of phencyclidine-induced violent behaviors, clinical psychiatrists, research psychiatrists and behavioral scientists do not know of the nature and cause of this aberrant behavior. It is not known, for example, if the psychotic-like behavior develops in virtually everyone who takes a sufficient amount of phencyclidine, or if it occurs in only a small proportion of the people who ingest phencyclidine. Neither is it known if there is a relationship between the bizarre emergence disorientation experienced by some people given ketamine or phencyclidine as an anesthetic, and the psychotic symptoms reported by users of phencyclidine. If the psychosis is limited to only certain individuals, it is not known what the predisposing conditions might be. The possibility that phencyclidine exacerbates a preexisting, perhaps subclinical tendency for psychosis has been entertained, but no firm conclusions on this point have been made. Unfortunately, there have been no recent developments in the treatment of either phencyclidine intoxication or long-term abuse.

Phencyclidine-induced psychosis has been touted as perhaps the best chemically-induced model of true schizophrenia (e.g., Javitt 1987). If this is true, and it is not even clear at this point that it is, it behooves behavioral scientists and clinicians to describe the

phenomenon better and provide sufficient, consistent information about it to allow it to be studied with greater precision.

NEW VISTAS

Information about the nature of the actions of substances related to phencyclidine has mushroomed. This is true despite the fact that there have been very few laboratory studies in human subjects; almost all of our information about phencyclidine comes from animal research. The chemistry, biochemistry, electrophysiology, and behavioral aspects of phencyclidine have become of extraordinary interest to a variety of disciplines. It is very likely that new drugs for treatment of neurological conditions and diseases may be derived from substances related to phencyclidine or with a similar mechanism of action. While it is not yet clear that this will in turn shed light on the characteristics of the pharmacology of phencyclidine abuse, it is at least possible that many new ideas will be brought forward that will be relevant to the treatment of phencyclidine acute intoxication, phencyclidine toxicity, or phencyclidine abuse.

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HEROIN, OTHER OPIATES, AND THE IMMUNE FUNCTION

INTRODUCTION

In the mid-1960s, the earliest clinical studies of heroin addicts resulted in abnormal physical and laboratory findings, suggesting that immune function impairment existed in a substantial portion (and perhaps the majority) of addicts. These findings included diffuse lymphadenopathy, elevated levels of serum proteins in the globulin fractions, marked elevations in levels of the immunoglobulins IgG and IgM, and a high prevalence of false positive tests for syphilis. These abnormalities were usually attributed to chronic intravenous injections of drugs (and adulterants and contaminants), to chronic liver disease, and to other infections resulting from the use of unsterilized injection equipment ("works") (Kreek 1973a, 1978, 1989, in press; Kreek et al. 1972). These early findings have been reviewed recently from a historical perspective, along with more recent clinical observations of

the untreated addict population, including persons who have acquired immunodeficiency syndrome (AIDS) (Kreek 1989, in press).

The first studies of chronic methadone treatment for narcotic addiction were performed at The Rockefeller University in 1964 (Dole et al. 1966; Dole 1988; Dole and Kreek 1973; Kreek 1973b; Kreek et al. 1976). These studies found that a single daily oral dose prevented narcotic withdrawal symptoms for 24 hours in most patients. Methadone was later shown to have a very prolonged half-life in humans (more than 24 hours) compared to the relatively short half-life of other narcotics (1 to 6 hours). Methadone could, therefore, eliminate "drug hunger" and associated drug-seeking behavior. Moreover, the high tolerance and cross-tolerance to other narcotics resulting from chronic methadone treatment prevented euphoria and other narcotic-like effects when other shorter acting opioids were used illicitly while the patient was in treatment (Dole et al. 1966). As a result, methadone maintenance treatment programs were widely initiated, first in selected general hospitals in New York City in 1965, and then more widely from 1967 to 1974.

With the widespread use of a safe and effective chronic treatment for narcotic addiction, studies of addicts' medical status and of the human physiological effects of methadone also proliferated and could be performed on a prospective basis (Kreek 1973a, 1978, 1989, in press; Kreek et al. 1972). Earlier findings of a high prevalence of lymphadenopathy, elevated serum proteins, and elevated serum immunoglobulin levels were confirmed. The presence of chronic liver disease in more than 60 percent of all patients studied also was further documented. Specific serological tests for hepatitis B markers found that liver disease in these patients was primarily the result of hepatitis B. Hepatitis B antigenimia was found in 5 to 15 percent of heroin addicts in treatment, and hepatitis B core and/or surface antibodies were found in 60 to 80 percent of addicts and former addicts in treatment (Kreek 1973a, 1978; Kreek et al. 1972). Many cases of chronic liver disease also were partly attributable to chronic alcohol abuse, an addiction found in 25 to 50 percent of heroin addicts seeking treatment (Kreek 1973a, 1978, 1979, in press; Kreek et al. 1972).

Several of these early prospective studies of methadone maintenance patients concluded that their serum protein and serum immunoglobulin abnormalities were not due solely to liver disease. Both the number of patients with immunoglobulin abnormalities and their abnormal elevation decreased the longer they remained in methadone maintenance treatment (Kreek 1973a, 1978, 1989, in press; Kreek et al. 1972).

By the mid- to late 1970s, more specific tests of different indices of immunological function were available. More extensive assessments of immunological function were performed on heroin addicts upon admission into and during chronic methadone treatment. Many of these studies were carried out by Barry Stimmel at the Mount Sinai Medical Center, Paul Cushman at the St. Luke's-Roosevelt Medical Center in New York City, and their colleagues. Abnormalities of T-cell function were found, including abnormal proliferative responses to mitogens and abnormal T-cell rosette formation. These abnormalities also decreased and immune system improved the longer patients remained in treatment (Kreek 1978, 1989, in press).

After specific opiate receptors and endogenous opioids (enkephalins, dynorphins, and endorphins) were discovered and first characterized in the 1970s, many research projects focused on the role of the endogenous opioid system under normal and pathological physiological conditions. Such studies have included the role of the endogenous opioid system in both normal and abnormal immunological function, and they have been extensively reviewed by Sibinga and Goldstein (1988). From the very first papers by Wybran, Cuatrecasas, and their associates, up to the present, there has been controversy over whether there are specific, classically defined, opiate receptors on cellular elements of the immune system, especially on lymphocytes. That is, are there stereoselective opioid binding sites, at which binding is

reversible by specific opioid antagonists (e.g., naloxone) which are coupled with an action of some type (Hazum et al. 1979; Sibinga and Goldstein 1988; Wybran et al. 1979)? Similarly, it still is not clear whether one or more specific endogenous opioids plays a role in controlling or modulating normal immune function, or in abnormal immune function (Morley and Kay 1986; Morley et al. 1987; Sibinga and Goldstein 1988; Weber et al. 1989; Weber and Pert 1984). Many reports present data defending each of these possibilities (Sibinga and Goldstein 1988).

RECENT RESEARCH ACCOMPLISHMENTS

There is increasingly good evidence that such specific hormones of classical endocrine function as cortisol in humans, and corticosterone in rodents, modulate specific aspects of immune function. Evidence also shows that neuropeptides, including many primarily involved in neuroendocrine function, may also directly modulate immune function (Blalock et al. 1985; Morley and Kay 1986; Morley et al. 1987; Plotnikoff and Murgo 1985; Sibinga and Goldstein 1988; Weber et al. 1989; Weber and Pert 1984; Weigent and Blalock 1987). Stress and other behavioral factors may alter immune function, very possibly by disrupting normal neuroendocrine function (Kreek 1989, in press; Shavit et al. 1985). Immune function may also modulate neuroendocrine function, both by paracrine and endocrine feedback loops, and the cellular elements of the immune system may be capable of neuropeptide production (Blalock et al. 1985; Weigent and Blalock 1987).

Role of Opiates and Opioids in the Immune System

The precise role of exogenous opiates in immune function, however, remains incompletely understood, as does that of endogenous opioids (Donahoe 1988; Sibinga and Goldstein 1988; Yahya and Watson 1987). Several articles published during the past 3 years have reviewed the interrelationship between heroin and other opioid use and immune function, including the relationship between immune function and neuroendocrine function and stress (Donahoe and Falek 1988; Morley and Kay 1986; Morley et al. 1987; Plotnikoff and Murgo 1985; Shavit et al. 1986; Sibinga and Goldstein 1988; Weber and Pert 1984; Weigent and Blalock 1987; Yahya and Watson 1987).

Evidence of altered immune function in methadone maintenance patients, along with studies of the endogenous opioid system's role in the normal physiology of the immune system, have led to increased interest in the effects of illicit opiates on immune function. These studies also have generated interest in the effects on cellular and humoral components of immune function of other long-acting synthetic narcotics such as LAAM (l-alpha-acetylmethadol), of short-acting narcotics used in pain management, such as morphine and meperidine, and of partial agonists, such as buprenorphine. Studies have focused primarily on the direct effects of some of these agents on immune function (Donahoe and Falek 1988; Yahya and Watson 1987).

Questions should also be raised concerning the indirect effects on immune function of each of these agents. Short-acting narcotics significantly alter neuroendocrine function. Persistent abnormalities of neuroendocrine function have also been observed in heroin addicts. Treatment with long-acting opioids such as methadone appears to normalize the abnormal neuroendocrine function found in heroin addicts (Kreek 1973a, 1978, 1987, 1989, in press). Opiate-induced abnormalities of neuroendocrine and endocrine function may, in fact, contribute to the immune function abnormalities seen in addicts. The chronic injection of foreign substances, as well as disease exposure (including liver disease), may also play an important or primary role. Normalization of immune function, observed in methadone maintenance patients, probably is primarily the result of reducing the multiple risks directly associated with intravenous drug use. However, it may also be due to the nor-

malization of neuroendocrine function that occurs in the methadone maintenance setting (Kosten et al. 1987; Kreek 1973a, 1978, 1987; Kreek et al. 1989).

Intensive studies of the possible effects on immune function of heroin and other exogenous and endogenous opiates and opioids are of particular importance in the present AIDS epidemic (Des Jarlais et al. 1985; Kreek 1987; Kreek et al. 1987; Novick et al. 1988). Intravenous drug abusers are the second highest risk group for AIDS and are rapidly becoming the highest risk group in such areas as New York and New Jersey. The profound effects of human immunodeficiency virus (HIV) infection on the immune system, even before development of AIDS, have been well documented. The effect of HIV on T4 cells and also on macrophages is clear. Thus, a more complete understanding of immune function status in both heroin addicts and former addicts in pharmacological or drug-free treatment prior to HIV infection is particularly essential (Des Jarlais et al. 1985; Kreek 1987, in press; Kreek et al. 1987; Novick et al. 1986a,b; 1988).

Several scientific groups have conducted a much needed wide spectrum of studies over the past 3 years to elucidate further the relationships of opioids, opiates, and immune function, and to determine the immune status of addicts and former addicts. Animal models also have been used, both in vivo and in vitro, to determine direct narcotic effects. In vitro research has also been done using human cells from healthy, normal control subjects as well as from patients receiving narcotics in treatment. This chapter summarizes recent accomplishments in this area reported during the past 3 years.

Falek and his colleagues have reported several important extensions of their earlier laboratory findings (Bueso-Ramos et al. 1988; Donahoe et al. 1987, 1988; Falek et al. 1986; Madden et al. 1987). Donahoe and his associates have identified coordinate, dependent, and independent effects of heroin, cocaine, and alcohol on T-cell E-rosette formation and on antigenic marker expression (Donahoe et al. 1987, 1986). In one of these studies, assays were carried out on cells of 21 heroin addicts entering treatment. None of the patients showed clinical evidence of hepatitis or AIDS-related disease, although 5 of the 21 had a significantly reduced T4:T8 ratio (Donahoe et al. 1988). Studies of T-cell E-rosette formation and of its kinetics were performed (Donahoe et al. 1986). This and earlier studies described how heroin use significantly depresses overall T-cell E-rosette formation (Donahoe et al. 1987, 1986; Kreek 1989, in press). However, the rates of T-cell E-rosette formation were significantly higher in heroin addicts who were also abusing cocaine. There was almost complete reversal of the usually observed depression of T-cell E-rosette formation in the cocaine-abusing, heroin-addicted subjects.

In heroin addicts who chronically abused alcohol in addition to cocaine, an intermediate level of T-cell E-rosette formation depression was found. In heroin addicts who had been heavy abusers of alcohol but had not used cocaine, a somewhat less depressed T-cell E-rosette formation was observed than in heroin addicts who drank less or not at all (Donahoe et al. 1986). These and earlier studies were interpreted as suggesting that opiates act directly upon T-cells to depress T-cell E-rosette formation by interfering with the normal, "microdisplacement" of E receptors from within the T-cell membrane. Similarly, it was hypothesized that cocaine reverses this effect by inhibiting intracellular influx of sodium ions and therefore altering the opiate interactions with sodium ions essential for disruption of the normal microdisplacement of receptors. It was suggested that the alcohol effects may be due to the well-established effects of alcohol on cell membrane fluidity, which could enhance receptor microdisplacement (Bryant et al. 1988; Dougherty et al. 1987). Thus, all three of these drugs may modulate the ligand binding capacity of T lymphocytes by affecting microdisplacement of the E receptors that are involved in rosette formation (Donahoe et al. 1987, 1986).

Based on other studies, Madden and colleagues have extended their earlier work attempting to determine whether there are specific, classical opioid

receptors on human T lymphocytes (Madden et al. 1987). Purified human T lymphocytes have a specific binding site for naloxone, a specific opiate antagonist, with a Kd for the site determined to be 50.62.4 nM. Naloxone is partially displaceable by a variety of opiate agonists, including morphine (56 percent), beta-endorphin (61 percent), and met- and leu-enkephalin (approximately 40 percent each), and the binding capacity of lymphocytes is found primarily in the membrane fraction after sonic lysis of cells (Madden et al. 1987). However, there was significant interindividual variability in the Bmax between different human lymphocyte samples. This may partially explain the variability of drug action often seen in different subjects.

One of the major differences between these studies and those previously carried out is that this group isolated mononuclear leukocytes from plateletpheresis residues obtained from the American Red Cross. These investigators found that platelet-free blood specimens yielded lymphocytes that would show specific binding for naloxone and that it was essential to purify the T lymphocytes to this point to show specific binding (Madden et al. 1987). This is thought to be due primarily to the binding of opiates by monocytes and/or platelets, or possibly to the binding of the specific opioids or their antagonists to erythrocytes or other contaminants present in blood specimens.

Parallel studies showed that, when platelet concentration is high (greater than 10 platelets per lymphocyte), a very high level of nonspecific binding is found, whereas when a lymphocyte preparation is used with a much lower platelet concentration, a significantly lower level of nonspecific binding occurs and specific binding could not be detected (Madden et al. 1987). In other studies, they showed that monocytes also had a very significant level of nonspecific binding for opioids. When this special monocyte and platelet-free preparation of lymphocytes was used, specific binding was 2 to 2.5 times greater than nonspecific binding. However, nonspecific binding was still a significant component of the total binding of naloxone by T lymphocytes.

The nonspecific binding was believed to be attributable in part to uptake by the lymphocytes of the naloxone. These studies represent the first in which a highly purified T lymphocyte preparation has been used and shown to bind naloxone in a saturable, competitive manner. However, as these investigators point out, the Kd found using naloxone is higher than that found in neuronal tissue for naloxone (approximately 50 nM versus 1 to 5 nM respectively). Thus, this relatively low-affinity binding occurs in a concentration range that has been shown in other studies to produce some changes in lymphocyte function. Whether or not high-affinity binding sites exist that are also involved in actions related to immune function has yet to be fully elucidated (Madden et al. 1987).

In still other studies, Donahoe and colleagues determined the comparative effects of morphine on leukocytic antigenic markers in both human and monkey cells (Bueso-Ramos et al. 1988; Donahoe et al. 1988). The technique of single- or two-color cytofluorometric analysis was used to determine the morphine effects on T11, Leu2a, and Leu3a antigen markers on leukocytes from humans and from rhesus monkeys. Using single-color analysis, the effects of morphine on the kinetics of T11 expression seemed to be similar using both human and monkey cells. Using two-color analyses, the simultaneous expression of T11 and Leu3a was uniform for both monkey and human cells, and the effects of morphine on the kinetics of expression of these markers varied only slightly between the two species (Donahoe et al. 1988). However, the distribution of Leu2a on T11 cells was markedly different between monkey and human T-cells, with all human Leu2a positive cells expressing similar numbers of T11 receptors, whereas monkey cells with high-density Leu2a apparently expressed fewer T11 markers than those with low-density Leu2a. The effects of morphine on the kinetics of Leu2a and T11 expression was also different in the two species, with morphine affecting primarily monkey T-cells, which simultaneously expressed Leu2a at high density

and T11 at low density. Thus, the effects of morphine on specific antigenic markers in rhesus monkeys and humans were profoundly different. These studies underscore the need to define carefully specific factors that may affect immune function in any species studied and to compare the findings with those obtained when human cells are used. This is a minimum requirement for extrapolating findings to the human situation (Donahoe et al. 1988).

During the past 3 years, the research groups headed by Sharp and Peterson at the University of Minnesota Medical School have also reported studies of the relationships of opioids and cellular and humoral elements of the immune system (Beyer et al. 1986; Peterson et al. 1987a,b; Sharp et al. 1987). Sharp and colleagues showed that in vitro beta-endorphin stimulates human polymorphonuclear leukocyte superoxide production by way of action at a stereoselective opiate receptor (Sharp et al. 1987). The cells were shown to be stimulated to release superoxide at beta-endorphin concentrations ranging from 10^{-14} to 10^{-8} M, with peak response occurring at 10^{-12} M. Hydrogen peroxide production was also measured. The accumulation of hydrogen peroxide was reduced by an inhibitor of production, nitroprusside, and by the converting enzyme, catalase (Sharp et al. 1987). When N-acetyl-beta-endorphin, an analog of beta-endorphin that does not bind to opiate receptors was used, in concentrations from 10^{-14} to 10^{-8} M, this inactive endorphin analog failed to cause superoxide accumulation (Sharp et al. 1987). Addition of the active enantiomer (l;-) of naloxone, 10^{-12} M, was shown to prevent the stimulatory effect of equal amounts of beta-endorphin on superoxide production; the inactive (d;+) enantiomer of naloxone was ineffective (Sharp et al. 1987).

The concentrations of beta-endorphin, around 10^{-12} M, that were shown in these in vitro studies to stimulate superoxide formation, are similar to the concentrations present in human peripheral plasma (Kosten et al. 1987; Kreek 1987, 1989, in press; Sharp et al. 1987). This demonstration that beta-endorphin can stimulate release of the reactive oxygen metabolites, both superoxide and hydrogen peroxide, by human polymorphonuclear leukocytes, at concentrations within normal range, is of potential physiological significance.

Sharp and colleagues point out that many opiate receptor mediator responses in other systems, including the guinea pig ileum, require opioid concentrations in a nanomolar range. This is significantly higher than the picomolar range effective here and present in circulating human plasma. In other studies of the responsiveness of the immune system to beta-endorphin in these lower concentration ranges (10^{-14} to 10^{-12} M), inhibition by low concentrations of naloxone was not observed, nor was stereoselectivity of the effects documented. However, the physiological significance, if any, of stimulation of polymorphonuclear leucocyte superoxide production by beta-endorphin is unclear. Although reactive oxygen metabolites may kill many pathogens and may cause genetic mutations in mammalian cells, they may also modulate the effects of specific cellular components of immune mechanisms (Sharp et al. 1987).

In addition to the findings with respect to beta-endorphin, Sharp and his group (1987) also showed that morphine yielded an essentially identical dose response pattern to beta-endorphin, with peak superoxide production by human polymorphonuclear leukocytes in response to morphine also occurring at concentrations of 10^{-12} M. However, no effect was observed when concentrations of 10^{-8} M of morphine were used. Only a modest effect was observed at 10^{-10} M and a minimal effect when 10^{-14} M concentrations of morphine were used. Thus, no effect was observed when morphine was added in its usual therapeutic concentrations. These studies could have some significance for treatment, either of chronic pain or for maintenance treatment of narcotic addiction, and may be pertinent to the effects of heroin as used in narcotic addiction. However, the concentrations of morphine or other opioids in these settings usually are in the 10^{-6} to 10^{-10} M range, a range where little or no effect of morphine was observed. One must assume that, as a physiological concentration of beta-endorphin (i.e.,

10^{-13} to 10^{-14}) had significant effects, this may be a normal or natural desirable effect. Whether or not this "normal" effect could be suppressed or reversed by therapeutic concentrations of morphine is not addressed in this study. During cycles of heroin addiction, levels of beta-endorphin may be suppressed and such a beta-endorphin effect might be reduced. During steady dose chronic methadone maintenance treatment, however, levels of beta-endorphin and their circadian rhythm become normal, and this possibly "normal" effect of beta-endorphin on superoxide production may also return. Therefore, if beta-endorphin has some physiological role in controlling superoxide production by human polymorphonuclear leukocytes, this normal response should be restored during chronic methadone treatment (Sharp et al. 1987).

In another sequence of studies carried out by Peterson, Sharp, and colleagues, opioid-mediated suppression both of cultured peripheral blood mononuclear cell respiratory burst activity and interferon gamma production has been demonstrated (Peterson et al. 1987a,b). These two studies were performed by the same research team and at about the same time as the previously cited studies. A departure was made in one aspect of the previous experimental design: The studies of the effect of beta-endorphin and morphine on superoxide production by polymorphonuclear leukocytes were performed acutely, with approximately 1 hour of incubation of cells. By contrast, the two studies of the effects of beta-endorphin on superoxide and gamma interferon production by peripheral mononuclear cells were carried out using cells cultured for a prolonged period of time—following incubation with beta-endorphin or morphine for 48 hours in most studies (Peterson et al. 1987a,b). It is not clear what assessments were made to determine whether beta-endorphin remained intact, without cleavage or degradation, and whether morphine remained intact and unmetabolized during these prolonged periods of cell culturing. The superoxide response to beta-endorphin detected in the study using human polymorpholeukocytes was described as "relatively modest" (Peterson et al. 1987a,b; Sharp et al. 1987).

In this second sequence of studies, opsonized zymosan and phorbolmyristate acetate were added to elicit a respiratory burst by the cells (Peterson et al. 1987a). Both morphine and beta-endorphin had a maximum inhibiting effect at concentrations similar to, but not identical with, those in the first study (Peterson et al. 1987a; Sharp et al. 1987). Morphine at a 10^{-10} M concentration, which had had only a modest effect in the previous study of polymorphonuclear leucocytes, appeared to be optimal, whereas beta-endorphin was studied at 10^{-12} M, a concentration in the optimal effective range, as before (Peterson et al. 1987a). It is of interest that when peripheral mononuclear cells were used, a dose response curve showed that maximal spontaneous superoxide production occurred following the addition of any amount of beta-endorphin in the range of 10^{-10} up to 10^{-14} M and any concentration of morphine from 10^{-6} to 10^{-10} M, but apparently with no significant effects from lower or higher concentrations. The observed inhibition by morphine and beta-endorphin of zymosan-stimulated superoxide production was indeed an opiate effect. This was shown by use of N-acetyl beta-endorphin, an analog of beta-endorphin without significant binding at classically defined opioid receptors, which gave no such effect, just as it had not caused any spontaneous release of superoxide in the studies of polymorphonuclear leukocytes. Naloxone was found to reverse this inhibition partially, but not completely, at equimolar concentrations.

The design of these studies was significantly different from the studies using polymorphonuclear leukocytes. Nevertheless, it would seem that both beta-endorphin and morphine have less of an effect on the spontaneous release of active oxygen metabolites from peripheral blood mononuclear cells than they do on release by polymorphonuclear leukocytes. Also, no dose response of any significance is observed when mononuclear cells are studied and inhibition of a stimulated response is the effect measured (Peterson et al. 1987a).

The time course of action of opioids exerting this inhibitory effect is also quite different. When peripheral blood and mononuclear cells were exposed to beta-endorphin for 1 to 2 hours, very little effect was observed, but when they were exposed for 48 hours there was a progressive increase up to 83 percent suppression of stimulated release of active oxygen metabolites (Peterson et al. 1987a).

Although plasma levels of beta-endorphin in humans fluctuate on a circadian basis, levels remain within the wide range used in these studies. All seem to suppress the active oxygen metabolite response to zymosan stimulation (Peterson et al. 1987a). In these studies, naloxone by itself had no effect on the zymosan-stimulated superoxide release, nor did it cause an increase in baseline superoxide productions. These findings are of interest in suggesting that the endogenous opiates remaining on the cells in culture were not exerting any tonic effects. However, the naloxone did partially block the inhibitory effects of morphine and beta-endorphin. Hydrogen peroxide, formed by superoxide dismutase catalyzed or spontaneous conversion from superoxide, was also found to be significantly increased by exposure to the opioids when the culture cells were not stimulated. However, hydrogen peroxide production in response to zymosan stimulation in the presence of opioids was reduced.

In further studies, adherence techniques were used to obtain populations of relatively pure lymphocytes and monocytes to study in addition to the mixed peripheral mononuclear cells. The purified lymphocyte preparations produced very little superoxide spontaneously, whereas the purified populations of monocytes produced significantly greater amounts of superoxide than did the mixed cell population (Peterson et al. 1987a). The unstimulated monocytes exposed to beta-endorphin produced significantly greater amounts of superoxide than unstimulated control monocytes or mixed mononuclear cells. The research team suggested that monocytes might be the principle target involved in this opioid-induced elevation of superoxide release. However, the primary effect under study, that of beta-endorphin inhibiting superoxide production by zymosan-stimulated cells, was observed only with mixed peripheral blood mononuclear cells and not with monocytes alone. To study this further, the supernatant from lymphocytes that had been cultured both in the presence and absence of beta-endorphin was added to a monocyte preparation, and it was found that the supernatant from beta-endorphin exposed lymphocytes significantly suppressed zymosan-stimulated superoxide production by purified monocytes. These findings suggest that there is a release of a factor from opioid exposed lymphocytes inhibiting any marked increase of superoxide production by monocytes in the presence of zymosan stimulation (Peterson et al. 1987a).

Cyclosporin, with and without beta-endorphin, was then added to the lymphocyte cell system. This polypeptide immunosuppressant blocked the inhibitory effect of beta-endorphin on superoxide production by peripheral nomonuclear cells in response to zymosan (Peterson et al. 1987a). Presumably, cyclosporin inhibits the release of some lymphocyte factor which, in turn, suppresses monocyte superoxide production response to zymosan. The physiological and pharmacological relevance of these data has yet to be elucidated. The data suggest that whereas opioids may stimulate baseline production of active oxygen intermediates by both polymorphonuclear leukocytes and peripheral mononuclear leukocytes, especially monocytes, opioids may also modulate or reduce such production in the setting of an external stimulus. Peterson and colleagues (1987) explain that this mononuclear microbial activity is in part dependent upon this "respiratory burst" activity, in which oxygen is metabolized rapidly to toxic metabolites, including the superoxide anion formation following acceptance of a single electron from NADPH. The opioid modulatory effect (inhibition of a stimulated response) seemed to result from both physiological and nonphysiological levels of beta-endorphin and from a very wide concentration range of morphine, including therapeutic concentrations. The data strongly suggest that these are classical specific opiate receptor mediated events (Peterson et al. 1987a; Sharp et al. 1987). The question

of whether or not pharmacological levels of morphine or its congeners would have any clinically significant inhibitory effect in the setting of stimulation has not been studied.

In another set of recent studies, it was discovered that both morphine and beta-endorphin could suppress production of the lymphokine interferon gamma by cultured human peripheral blood mononuclear cells (Peterson et al. 1987b). Because interferon gamma normally produced by activated T lymphocytes and by natural killer cells activates macrophages and also has other immune functions, this suggests that such a suppression of gamma interferon could lead to decreased macrophage activity. Peripheral blood mononuclear cells containing 15-38 percent monocyte and 60-85 percent lymphocyte were used for most studies; in other studies monocytes were isolated to a final preparation containing more than 95 percent monocytes. In some studies, a preparation containing 97 percent lymphocytes was used. Cells were first exposed for 1 to 24 hours with opioids or ACTH, with or without a 30-minute preincubation with the opioid antagonist naloxone, and then incubated with optimal doses of concanavalin A or varicella virus to maximize interferon gamma production. Maximal suppression of gamma interferon production by opioids in the setting of concanavalin A stimulation of peripheral blood mononuclear cells was found with concentrations of beta-endorphin from 10^{-12} to 10^{-10} M and concentrations of morphine from 10^{-12} to 10^{-6}, within physiological and pharmacological therapeutic ranges respectively. Concentrations of beta-endorphin and also ACTH which had inhibitory effects included both the physiological and pathological range, from 10^{-12} to 10^{-10} M; lower concentrations including low physiological levels, 10^{-18} to 10^{-14}, had no effect. In control stimulated cells, concanavalin A caused production of gamma interferon which was reduced approximately 50 percent when ACTH were added. Both morphine and beta-endorphin caused a similar 50 percent reduction of gamma interferon production. A much lesser suppression of gamma interferon by opioids was found when only 1 hour of exposure was used; no greater suppression after 24 hours of opioid exposure was observed. However, removal of the opioids by washing after the 3-hour incubation eliminated the suppressive effect. This suggests that continued opioid or ACTH presence was essential, at least for maximal effect.

As in their previous studies, the researchers carried out careful experiments to determine the effects of naloxone and also N-acetyl-beta-endorphin. These studies demonstrated antagonism by naloxone and need for an intact amino-terminus of beta-endorphin to achieve the inhibitory effect. This suggests that activity at a classical specific opiate receptor was involved in this effect. A synthetic analog of enkephalin, (D-Ala2)-met-enkephalinamide, consistently suppressed interferon gamma released to a much greater extent than either beta-endorphin or ACTH. A 10^{-14} concentration was optimal, suggesting that more than one opiate receptor may be involved in this action. The investigators went on to demonstrate that the addition of catalase to remove hydrogen peroxide, or of superoxide dismutase, to act as a scavenger of superoxide, prevented the inhibition of gamma interferon production by opioids. These findings suggest that opioid-induced enhancement of superoxide production by monocytes in vitro may lead to the inhibition of gamma interferon production by activated T lymphocytes and natural killer cells.

Peterson and colleagues (1987) also found that prostaglandin metabolites, possibly PGE, released by monocytes, were involved in the observed opioid suppression of gamma interferon production. Indomethacin added in vitro, or administered to volunteer subjects 2 to 3 days before peripheral blood mononuclear cells were obtained for study, inhibited the suppressive effect of beta-endorphin and morphine on gamma interferon production in vitro. The fact that essentially physiological concentrations of natural opioid peptides, or synthetic analogs of natural peptides, had significant effects, suggests a possible role of the endogenous opioids and ACTH peptides in modulating gamma interferon production. These findings may or may not suggest that a pathological state

would pertain in the setting of exposure to large amounts of exogenous opioids.

In all of the laboratory studies discussed above, the findings suggest that both opiates and endogenous opioids in vitro at pharmacological and physiological concentrations may have specific effects on lymphocytes. These, in turn, may lead to responses in lymphocytes that may affect monocyte activity or some other humoral or cellular aspect of immune function. In each of these studies, effects have been observed at relatively modest concentrations that could be considered to be physiological for the endogenous opioids, or in therapeutic range for narcotic analgesias, with or without similar effects observed when higher concentrations are used. Thus, it is not clear whether these effects are relevant to pathological states, such as the immunological abnormalities observed in heroin addicts. These observations suggest, however, that the endogenous opioids may have modulatory effects in the normal physiology of the immune system.

Beyer and colleagues (1986) found that very high levels of beta-endorphin may alter the effects of ACTH at the level of the adrenal cortex with respect to the usual response of increasing cortisol release. When very high doses of beta-endorphin were infused prior to ACTH infusion, the cortisol responsiveness was significantly reduced. However, an intravenous bolus administration of beta-endorphin (100 µg) did not have this effect, which was achieved only with a 30-minute intravenous infusion of even larger total amounts of beta-endorphin (at a rate of 1 µg/kg per minute). The intravenous bolus dose achieved a plasma beta-endorphin concentration of 5,000 pg/mL. The intravenous infusion technique resulted in a plasma beta-endorphin concentration of 100,000 pg/mL, far higher than has ever been observed in any physiological (around 2 to 35 pg/mL) or pathological (around 35 to 300 pg/mL) state (Kosten et al. 1987; Kreek 1987). Therefore, these studies may be of mechanistic interest, but have little relevance with respect to the effects of circulating beta-endorphin from the anterior pituitary in humans. These findings could have some implications if beta-endorphin is shown to be released in high concentrations from elements of the lymphoid system (as has been suggested recently) and, thus, could exert a paracrine effect, either at the adrenal cortex or at some other local site of action (Weigent 1987; Blalock 1985).

Some additional studies related to this topic have been reported by investigators who have been supported in part by the National Institute on Drug Abuse (NIDA) extramural program. Hemmick and Bidlack (1987) studied calcium uptake by rat thymocytes in the setting of mitogen stimulation with and without the addition of the endogenous opioid beta-endorphin. Although immunostimulatory and immunosuppressive effects reportedly have been caused by several endogenous opioids, data concerned with cellular mechanisms of such actions are limited. There is some indirect evidence of the involvement of the adenylate cyclase pathway; at the same time, other studies have suggested that cyclic AMP or cyclic GMP systems are not playing a major role (Hemmick and Bidlack 1987). Hemmick and Bidlack questioned whether another parallel system cellular signal transduction mechanism, that of modulation of calcium influx, is involved. They point out that an early event associated with the activation of lymphocytes by mitogens is the influx of small, but measurable, amounts of calcium. They also cite reports that there are voltage-independent ionized calcium channels in helper T lymphocytes and that physiological stimulation of lymphocytes (including the activation of T lymphocytes, by antigens, by monoclonal antibodies, or by chemotactic substances) is accompanied by an increase in intracellular calcium. Activation or proliferation of lymphocytes is blocked by the prevention of this calcium influx (Hemmick and Bidlack 1987).

To study the possible effects of endogenous and exogenous opioids on calcium uptake by thymocytes, which are the precursors of T lymphocytes, a technique of $^{45}Ca^{2+}$ uptake assay was used in the absence and in the presence of various T-cell mitogens, including concanavalin A and phytohemagglutinin. When

beta-endorphin was added after 1 hour of incubation with the mitogen, it was shown that beta-endorphin significantly enhanced the calcium uptake, using concentrations from 10^{-10} up to 10^{-5} M. However, no further stimulation was found when beta-endorphin was added to phytohemagglutinin-stimulated thymocytes.

Naloxone did not reverse this enhancement by beta-endorphin, which suggests that classical opiate receptors were not involved. Naloxone alone had no effect on this system. Further studies showed that modest and very high concentrations of exogenous opiates, including morphine, etorphine, and codeine, had no effects on this system. No effects were found when dynorphin analogs, enkephalin analogs, and other analogs of beta-endorphin, including those with blocked amino- or carboxy-terminus, as well as shorter fragments of beta-endorphin, were used. Therefore, this effect seems to be limited to beta-endorphin 1-31 and occurs only in the setting of stimulation with concanavalin A. This stimulates both mature and immature thymocytes, whereas the phytohemagglutinin stimulates only mature thymocytes and circulating T lymphocytes. Hemmick and Bidlack (1987) postulate that this beta-endorphin effect may be limited to immature thymocytes and have no relevance for circulating T-cells which are mature lymphocytes. The relationship of this observed action of beta-endorphin in modulating the mitogen-stimulated calcium uptake by rat immature thymocytes to normal human physiology, or in narcotic addiction, remains to be clarified.

Effects of Stress on the Immune System

Stress is known to alter the activity of some of the endogenous opioids. Stress also has been documented, in both animal models and humans, to modulate immune function. The connection between these two phenomena has been studied by many researchers. In a recent paper from one extramural NIDA-supported program, Jessop and colleagues (1987) have considered the effects of prolonged exposure to stress on rat lymphocyte proliferation. They found that rats exposed to 5 weeks of isolation and to scheduled, limited water consumption demonstrated a significantly enhanced splenic lymphocyte proliferation response to phytohemagglutinin compared to group-housed animals maintained under standard conditions, with free water access. When either of the stressors, isolation or scheduled water supply, was used, enhanced lymphocyte proliferation in response to mitogen was observed. When rats were exposed to both stresses for 12 weeks, blood and splenic lymphocyte responses were enhanced more than two- and threefold, respectively. However, at the time of sacrifice, no significant changes were found either in total white blood cell counts or in plasma corticosterone levels. The total body weights of the animals maintained in isolation with water restriction were significantly lower than those of the group-housed animals. It was concluded that, whereas acute exposure to stress may result in immunosuppression, chronic exposure to stress in animal models may result in immune enhancement. It was further postulated that acute exposure to stress may result in an increase in adrenal activity, with resultant release of glucocorticoids, catecholamines, and opioid peptides. However, no hypothesis was formed as to what may cause the enhanced lymphocyte activity in the setting of chronic stress. An initial significant reduction was found in the response of splenic lymphocytes to phytohemagglutinin within 48 hours after isolation, but there was an enhanced response after 5 weeks of chronic stress (Jessop et al. 1987). The researchers suggest that the response seen in this study might be due to both increased numbers and increased sensitivity of splenic lymphocytes. The relevance of these findings to human clinical situations has yet to be elucidated.

IMMUNOLOGIC PROFILE OF HEROIN ADDICTS AND THE ROLE OF AIDS AND OTHER INFECTIONS

Immunological abnormalities, especially abnormalities in B-cell function, reflected by significantly increased levels of IgM and IgG, were first reported in heroin addicts in the mid-1960s and again in the 1970s; abnormalities of immunoglobulins were also found in prospective studies of methadone maintenance patients, but there were both decreases in the numbers of patients with abnormal levels and decreasing actual abnormal levels with time in treatment (Kreek 1989, in press). Several early studies of heroin addicts entering methadone maintenance treatment and, in some cases, followed prospectively during treatment, reported abnormalities in T-cell function as reflected by abnormal T-cell rosette formation, but again decreasing numbers of patients had these abnormalities as time in treatment increased (Donahoe and Falek 1988; Donahoe et al. 1986; Kreek 1989, in press). The discovery of the endogenous opioids and their receptors led to considerable research on the possible role of the endogenous opioids in the normal modulation of immune function, as well as the effects of possible derangements of the endogenous opioid system on immune function (Blalock et al. 1985; Hazum et al. 1979; Morley and Kay 1986; Plotnikoff and Murgo 1985; Shavit et al. 1985; Sibinga and Goldstein 1988; Weber et al. 1989; Weber and Pert 1984; Weigent and Blalock 1987; Wybran et al. 1979).

The AIDS epidemic led to a renewed interest in the immune status of current heroin addicts and former addicts in methadone maintenance treatment, as the relationships of this immune status to HIV infection and AIDS had become of obvious importance (Des Jarlais et al. 1985; Kreek 1987; Kreek et al. 1987; Novick et al. 1986a,b,c). There was an early recognition that the primary pathology in AIDS involves the disruption of immune function and profound immune suppression, preceded by infection of both macrophages and T4 cells by the HIV virus. Immunological abnormalities in intravenous drug abusers, specifically those related to chronic alcohol abuse coupled with alcoholic liver disease, have been identified as a cause of false positive tests for the HIV antibody, the most common serological test used in surveys and in individual evaluation for HIV infection (Novick et al. 1988). However, Western blot analysis may be used in this setting to determine the presence of true HIV infection (Novick et al. 1988).

In the past 6 years, there have been numerous clinical reports concerning possible abnormalities of immune function in heroin addicts, ranging from lymphadenopathy, to abnormal lymphocyte counts, abnormal absolute T lymphocyte numbers, abnormal T-cell subset absolute numbers, and abnormal functioning of B-cells, T-cells, and natural killer cells. However, very few reports have considered whether HIV infection was present. Many reports appeared before HIV infection was widely recognized in the particular locations where the studies were performed. Few studies considered the possible effects of polydrug abuse, intravenous versus nonintravenous drug abuse, the presence of liver disease, especially hepatitis B and hepatitis delta, and other factors relevant to any immunological abnormalities observed. In some studies, there has been a presumption that the major drug of abuse itself, or a pharmacological agent used in the treatment of drug abuse, may have caused the abnormalities observed. However, a few recent studies have addressed the multiple variables that may affect immune function in the intravenous drug abuser, particularly the heroin addict and the former heroin addict in treatment.

Des Jarlais and colleagues (1985) reported a study of intravenous drug users, primarily heroin addicts, some of whom concomitantly abused cocaine, and some of whom were infected with HIV. Total lymphocytes and lymphocyte subsets, including total B-cells and T-cells, and absolute numbers of T-cell subsets and immunoglobulins reflecting B-cell function, were measured. The focus of this study was a comparison of lymphocyte immunoglobulin levels of HIV-positive (ELISA test positive confirmed by Western blot analysis) and HIV-negative subjects.

Lymphocytosis was significantly greater in the HIV-negative group, and the absolute numbers of B-cells and T4 helper cells were significantly greater in the HIV-negative group. Conversely, T8 suppressor cells were significantly higher in the HIV-positive group and the T4:T8 ratio was significantly lower in the HIV-positive group. Although immunoglobulins IgG and IgM were above normal in both the HIV-negative and HIV-positive group, the IgG levels were significantly higher in the HIV-positive group. This reflects nonspecific hyperactivity of B-cell function as compared with the HIV-negative group.

Novick and colleagues (1986c) were interested in the possible role of intravenous heroin self-administration (usually with unsterile needles and other injection equipment), and the intravenous injection of foreign substances used to extend heroin, in exposure to multiple diseases. They contrasted the effects of self-injection on immune response with those of smoking or paranasal heroin administration, comparing the absolute numbers of T lymphocytes and subsets in intravenous and nonintravenous heroin abusers. This study was carried out in London, presumably prior to the AIDS epidemic. The T4:T8 ratios of the two groups did not differ significantly from each other or from the mean value found in normal subjects. However, 2 of 14 intravenous drug abusers and 2 of 10 nonintravenous drug abusers had T4:T8 ratios less than 1.2; one case was less than 0.95. Novick and colleagues also found that there were no differences in the absolute numbers of T3, T4, or T8 cells between the two groups. The duration and quantities of the heroin used in the two groups, as well as other demographic characteristics, were similar.

In an attempt to sort out the variables further, Novick and colleagues (1986a) looked at the effects of chronic hepatitis B viral liver disease and sexual preference on T lymphocyte subsets. In this study, 15 homosexual and 11 heterosexual men with chronic hepatitis B virus infection were compared with 11 homosexual and 16 heterosexual men in apparently good health (i.e., with no markers for hepatitis B infection). The hepatitis B group comprised patients showing hepatitis B surface antigenemia for more than 6 months and elevated levels of serum transaminases reflecting hepatocellular necrosis. Four patients had evidence of HIV infection. When these patients were evaluated as a subgroup, they had significantly lower T4:T8 ratios and significantly higher absolute numbers of T3 cells and T8 cells than the remaining 49. When the homosexual subgroup was analyzed separately, it was found that the T4:T8 ratios were significantly lower in the heterosexual group, independent of hepatitis B virus infection. This lowered T4:T8 ratio was accounted for by a significant increase in absolute numbers of T8 cells. Chronic hepatitis B infection was not found to be associated with any significant abnormality of T lymphocyte subsets or of natural killer cell activity when analyzed independently of sexual preference. Abnormalities in these immune indices found in subjects who were both homosexual and positive for hepatitis B surface antigen and hepatitis e antigen were not significantly different from the abnormalities in the cellular immune function found in homosexuals without hepatitis B or HIV infections.

Natural killer cell activity was also found to be significantly reduced in homosexual men independent of hepatitis B infection. Of the subjects with chronic hepatitis B surface antigenimia, 23 of the 26 had liver biopsies. Chronic active hepatitis with or without cirrhosis was found in 12 of the 26. This may account for the fact that all of the abnormalities of cellular immune function found in this study were independent of chronic hepatitis B infection.

Effects of Methadone Maintenance on Immune Function

In a study of unselected methadone maintained patients in treatment for periods ranging from 1 month to more than 10 years, some patients had abnormalities in T-cell subsets including elevations in T3, T4, and T8 (Kreek et al. 1989). In this unselected methadone maintenance group, patients had T4:T8 ratios intermediate between those found in the studies of other New York and London intravenous heroin addicts.

Both the London heroin addicts and the unselected New York methadone maintenance patients had a mean T4:T8 ratio. This is within normal limits, in contrast to a study of heroin addicts in New York, in whom the mean T4:T8 ratio was significantly lowered. These studies suggest that partial or complete normalization of absolute numbers of T-cells and T-cell subsets as well as T4:T8 ratios may occur during methadone maintenance treatment (Des Jarlais 1985; Kreek et al. 1989; Novick et al. 1986c).

Another study by Novick and colleagues (1988) suggests that normalization improves with length of time in methadone maintenance treatment. In this highly controlled study, HIV-negative intravenous heroin addicts were compared with very long-term, HIV-negative methadone maintenance patients. The methadone group had been on moderate to high doses of methadone (mean dose 40 mg per day) for 11 to 21 years (the median was 16 years). None was an alcohol, cocaine, or polydrug abuser at the time of the study. Both groups were compared with healthy control subjects. The absolute total number of T-cells (T3), was significantly elevated in the intravenous heroin users, but normal in the long-term methadone maintenance patients. Similarly, absolute numbers of T4 and T8 subsets were significantly elevated in the active intravenous heroin addicts, and both were normal in the long-term methadone maintenance patients.

These studies provide important evidence that long-term, moderate to high dose methadone treatment allows normalization of the immunological abnormalities found in heroin addicts without HIV infection. In the Novick and colleagues (1988) study, the history of liver disease, and the serological and biochemical evidence of chronic liver disease, were similar in the heroin addict and methadone groups. In both groups, the presence of liver disease and related biochemical abnormalities was significantly different from the normal control group. Therefore, the presence of liver disease, resulting primarily from hepatitis B infection, apparently was not responsible for the immunological abnormalities found in the heroin addict group.

The unselected methadone patients, in treatment from 1 month to 10 years, with or without ongoing alcohol, cocaine, or polydrug abuse, and with unknown HIV status, had absolute numbers of T-cells (T3) and T-cell subsets (T4 and T8) that were intermediate between the active heroin addicts and the very long-term, HIV-negative methadone patients without ongoing alcohol or polydrug abuse (Kreek et al., in press).

Quantitative serum immunoglobulin levels have also been performed in several of these recent studies, both in HIV-positive and HIV-negative heroin addicts, and in former heroin addicts in methadone maintenance treatment (Des Jarlais et al. 1985; Novick et al. 1988). It was shown that in the HIV-positive active addicts, levels of serum immunoglobulin G (IgG) were significantly higher than in HIV-negative active heroin addicts (Des Jarlais et al. 1985). Also, active heroin addicts had significantly higher levels of IgG than healthy control subjects. The serum IgG levels of very long-term methadone maintenance patients (11 years or more) were neither significantly greater than those of healthy control subjects nor significantly lower than those of parenteral heroin addicts (Novick et al. 1988).

It was shown that levels of serum immunoglobulin (IgM) were not different from each other in HIV-positive versus HIV-negative active intravenous heroin addicts and were significantly greater than those of both healthy control subjects and very long-term methadone maintained patients (Des Jarlais et al. 1985; Novick et al. 1988). Notably, the very long-term methadone maintenance patients were not significantly different from the healthy control subjects (Novick et al. 1988). Although earlier studies found improvement in both IgM and IgG levels during methadone maintenance treatment, the Novick and colleagues (1988) study is the first to show complete normalization of IgM levels during long-term methadone maintenance treatment in patients without significant polydrug or alcohol abuse, but with chronic liver disease approximately as prevalent as in the active heroin addicts.

Natural killer cells are the first line of defense against many viral infections and many types of tumor invasion, and natural killer cell cytotoxicity does not require previous exposure to the antigen to exert these cytotoxic effects. Therefore, this aspect of immune function may be especially important in modulating the rate of progression from HIV infection to AIDS. It is not known whether natural killer cell activity plays any role in the initial HIV infection, although this is less likely. Natural killer cell activity in active former heroin addicts and also former heroin addicts in methadone treatment has been studied extensively over the past 3 years (Kreek 1989, in press; Kreek et al., in press; Nair et al. 1986; Novick et al. 1988; Ochshorn et al. 1989). These studies, similar to earlier studies, report that natural killer cell activity is significantly lowered in unselected heroin addicts, even HIV-negative, active addicts. In most recent studies, homosexual subjects have been either excluded or considered a separate subgroup for data analysis, as it has been documented that natural killer cell activity may be significantly lowered in homosexuals without any apparent HIV infection and without chronic hepatitis B virus infection (Novick et al. 1986a). One well-controlled study used only HIV-negative subjects and found that natural killer cell activity is significantly reduced in intravenous heroin addicts. Three effector:target ratios were used to measure natural killer cell activity (100:1; 50:1; 25:1) (Novick et al. 1988). Long-term methadone maintenance patients, in treatment on moderate to high doses of methadone for 11 years or more, and HIV-negative, had natural killer cell cytotoxicity activity that was normal at all effector target ratios studied.

In a preliminary study of 34 unselected methadone maintenance patients in treatment for 1 month to 10 years, with or without polydrug or alcohol abuse, 53 percent of subjects had normal natural killer cell activity, 21 percent had natural killer cell activity greater than two standard deviations below normal, and 26 percent had natural killer cell activity greater than three standard deviations below normal (Ochshorn 1989). In an extension of this research, natural killer cell activity was measured in 47 unselected methadone maintenance patients in a single clinic; 57 percent had normal natural killer cell activity. However, the entire study group had a mean natural killer cell activity significantly below normal at all three effector:target ratios used (100:1; 50:1; 25:1) (Kreek et al., in press). In this study of unselected methadone maintenance patients, HIV status has not yet been determined because of multiple ethical and practical constraints, including patients' desire to be tested, limitations of active, supplementary pre- and post-HIV test counseling, and the special counseling needed in the setting of finding positive HIV results (Kreek et al., in press). However, other studies carried out in New York City in 1983 and 1984 have shown that fewer than 10 percent of patients entering methadone maintenance treatment prior to 1978 were HIV-positive in 1984. Fifty percent to 60 percent of street heroin addicts and methadone maintained patients entering treatment after 1983 are HIV positive (Novick et al. 1986b). It is estimated that the prospective study population of unselected methadone maintained patients described above will have approximately a 30 percent HIV-positive rate (Kreek et al., in press).

Although natural killer cell activity reportedly is lowered in the presence of AIDS, the time course of lowering of natural killer cell activity after HIV infection and the progression to AIDS has not yet been defined. These findings in unselected methadone maintenance patients suggest that normalization of natural killer cell activity can occur during methadone maintenance treatment and does occur in over 50 percent of patients during short to intermediate term treatment (Kreek et al., in press; Ochshorn et al. 1989). The study of very long-term methadone maintenance patients suggests that when HIV infection has not occurred, a restoration of normal natural killer cell activity is possible in all patients (Kreek et al., in press; Novick et al. 1988; Ochshorn et al. 1989). The absolute numbers of cells bearing natural killer cell markers were also normal in the very long-term methadone maintenance patients (Novick et al. 1988).

It is now known that complete normalization of natural killer cell activity occurs during extended

methadone maintenance treatment despite greater opioid exposure than during cycles of heroin addiction. Normalization of natural killer cell activity also occurs in more than 50 percent of methadone maintenance patients, irrespective of HIV status or of other drug abuse. It is therefore unlikely that narcotics themselves cause the lowering of natural killer cell activity consistently observed in heroin addicts not in treatment (Kreek 1989, in press; Kreek et al., in press; Novick et al. 1988). Restored killer cell activity is probably the result of such factors as cessation or significant reduction of use of unsterile needles and other injection equipment, concomitant elimination of exposure to a variety of drug contaminants and extenders, and reduced exposure to intravenously injected infectious disease agents. Yet it is also possible that, during cycles of heroin addiction, the well-documented disruption of neuroendocrine function by heroin may contribute to diminished immune function, including natural killer cell activity.

EFFECTS OF HORMONES ON THE IMMUNE SYSTEM

There is increasing evidence that both peptide and steroid hormones normally modulate various cellular and humoral components of immune function (Blalock et al. 1985; Kreek 1989; Morley and Kay 1986; Morley et al. 1987; Weigent and Blalock 1987). Normalization of most aspects of neuroendocrine function occurs during chronic methadone treatment (Kosten et al. 1987; Kreek 1973a, 1978, 1987, 1989). To explore further the possible role of the endogenous opioids in tonic modulation of natural killer cell function, in vitro studies have been performed in which the specific opiate antagonist, naloxone, in its active (l;-) enantiomer, was added to the natural killer cell assay over a wide concentration range. These have included high concentrations known to displace endogenous opioids from both delta and kappa as well as from mu receptor subtypes by this mu-preferring ligand. These concentrations have far exceeded those needed for displacement of endogenous opioids from all three receptor subtypes and are higher than in therapeutic use. The active enantiomer of naloxone did not alter natural killer cell activity when concentrations up to 10^{-4} M were used in these in vitro studies (Oschshorn et al. 1988). When the inactive enantiomer of naloxone (d;+) was used in similar in vitro studies, the same results were obtained. That is, no alteration in natural killer cell activity was observed until concentrations equal to or greater than 5×10^{-4} M were reached.

To address directly the question of a possible effect of methadone on natural killer cell activity, similar in vitro studies have been performed (Kreek, in press; Oschshorn et al, in press). In these studies of an opioid agonist, there were similar findings to those obtained from studies of the antagonist naloxone. No effects on natural killer cell activity were observed when methadone concentrations up to 10^{-5} M were used. However, with concentrations of 10^{-4} M or greater, a significant decrease in natural killer cell activity was observed (Oschshorn et al., in press). Again these concentrations are much higher than those achieved in normal clinical use. Similar results were found when the active (l;-) and inactive (d;+) enantiomers of methadone were studied separately (Kreek, in press; Oschshorn, in press). Intact cells were documented at the end of incubation periods in each of these studies, even when very high concentrations of opioid agonist or antagonist were used. It is therefore hypothesized that these exogenous opioid agonist and antagonist ligands have some nonspecific but nontoxic effect on cell membranes. This is not dependent on binding to a specific "classical" opiate receptor (i.e., stereoselective binding of opioids, with saturability displacement of agonists by a specific opioid antagonist and coupled with a biological action). The reduction of natural killer cell activity found at very high concentrations of active and inactive opioid alkaloid compounds is not a classical opioid receptor mediated effect.

Several research teams have previously reported that one endogenous opioid, beta-endorphin, can significantly enhance natural killer cell activity in vitro

(Kay et al. 1987; Krant et al. 1986; Kreek 1989, in press; Mandler 1962; Morley and Kay 1986; Prete et al. 1986; Sibinga and Goldstein 1988). Controversy still exists as to whether any of the other endogenous opioids has this effect and also whether morphine has any effect on natural killer cell activity in vitro (Kay et al. 1987; Krant and Greenberg 1986; Kreek 1989, in press; Mandler 1962; Morley and Kay 1986; Prete et al. 1986; Sibinga and Goldstein 1988). Some investigators have shown that the enhancement of natural killer cell activity by beta-endorphin is a naloxone reversible effect, suggesting action at a specific "classical" opiate receptor. However, these reports and others have presented conflicting data concerning whether endogenous opioid peptides or exogenous opiates can enhance natural killer cell activity in vivo. Specific opiate receptors have not been detected on isolated natural killer cells. The normalization of beta-endorphin and the circadian rhythm of levels of beta-endorphin, which occurs during methadone maintenance treatment, could contribute to the concomitant normalization of natural killer cell activity (Kosten et al. 1987; Kreek 1973a, 1978, 1987, 1989, in press). During heroin addiction, beta-endorphin levels become suppressed and circadian rhythms of levels disrupted following administration of this short-acting opioid (Kreek 1978, in press).

FUTURE DIRECTIONS

Cocaine abuse by heroin addicts receiving methadone maintenance as well as those not receiving methadone maintenance is increasingly common, as it is among nonaddicts (Kreek 1987). Acute administration of cocaine to cocaine abusers under controlled conditions in a clinical research setting has been shown to cause a transient, though significant, increase in natural killer cell activity (Dyke et al. 1986). This increase is brief, paralleling the half-life of cocaine. Restoration to normal natural killer cell activity occurs within 2 to 3 hours (Dyke et al. 1986). The possible clinical implications of these findings are of interest. In studies of unselected methadone maintained patients, subgroup analyses were carried out to determine whether or not there were any significant differences between methadone maintained patients known to use cocaine and those who did not. No differences of significance were found with respect to natural killer cell activity. However, blood specimens to determine natural killer cell activity in vitro were rarely, if ever, obtained within 2 hours of cocaine use. In the studies of very long-term methadone maintenance patients, none was a cocaine abuser (Novick et al. 1988).

More studies employing in vitro systems with cells from multiple animal species, as well as normal human cells, are also needed. These would help clarify the direct effects of heroin, other drugs of abuse, and therapeutic agents used to treat drug abuse on cellular and humoral components of immune function. Studies using whole animal models to determine interactive and indirect drug effects are also needed. It is also imperative to study healthy human subjects, contrasting them with heroin addicts and other specific, well-defined drug abuser groups. Studies of patients being treated with agents such as methadone are also needed to determine the effects of these agents on immune function. Both direct and indirect drug effects must be carefully considered.

Research on the effects of stress on specific cellular and humoral components of immune function and of the role of endogenous opioids in both avoidable and unavoidable stress are also pertinent to heroin and other drug abuse. Such research is essential to designing, executing, and interpreting urgently needed animal and human immunological studies (Kreek 1989, in press; Morley and Kay 1986; Morley et al. 1987; Plotnikoff and Murgo 1985; Shavit et al. 1986a,b 1985; Sibinga and Goldstein 1988; Weber et al. 1989, 1984; Yahya and Watson 1987). Research indicating that such factors as exercise and aging may affect endogenous opioids or opioid-induced immune function changes is also pertinent (Fiatatone et al. 1988; Kreek 1989, in press; Norman et al. 1988).

Over the past 3 years, a great deal of research has been conducted on the relationships between various specific neuropeptide and peripheral hormones and the immune system, as well as on the role of endogenous opioids and exogenous opioids on specific indices of immune function. Bryant and colleagues (1987, 1988a,b) recently studied temporal relationships between morphine administered by pellet to a mouse and the subsequent immune responses observed. At 48 and 72 hours after implantation of a morphine pellet, suppression of T lymphocyte proliferation in response to the mitogen concavalin A was found. However, this effect was no longer present at 96 hours and 120 hours after morphine pellet implantation. At those times when tolerance to other morphine effects could be demonstrated, there was an enhancement of the T-cell proliferative response to concanavalin A.

Proliferation of B-cell lymphocytes in response to lipopolysaccharide was also studied by Bryant and colleagues (1987, 1988a,b). This response was found to be even more sensitive to implanted morphine pellets. Suppression of response was found at 24, 48, and 72 hours after implantation. After 72 hours no differences were found between morphine and placebo-implanted animals. In these studies, the suppression of mitogen-induced proliferation of both T and B-cells, which was accompanied by atrophy of immune organs, was only a transient effect. No effect, or the opposite effect, was observed at later time points, when tolerance had developed to the antinociceptive effects of morphine pelleted mice. Adrenal hypertrophy was found in the chronic morphine pelleted mice, suggesting to these investigators that acute alteration of endocrine function by morphine might have been related to the altered immune effects observed. The investigators also related this morphine-induced immunomodulation partly to stress. The rapid development of tolerance or adaptation to the morphine-induced alterations in immunological indices observed raises the question of whether the endogenous opioids, and whether chronic heroin use or methadone maintenance treatment in humans, play any physiological roles. Morphine-induced immunomodulation was not found to be related to serum morphine concentrations, but rather to the length of time following initiation of exposure to morphine (Bryant et al. 1988b). Tolerance to diverse morphine effects seems to be the most likely explanation for the transient nature or even the bidirectional changes of immunomodulation observed.

Other studies have focused on the relationships between the humoral elements of the immune system and classical neuroendocrine and peripheral endocrine function (Bernton et al. 1987, 1988). Interleukin-1, produced by macrophages and monocytes experimentally in response to endotoxin, was found to cause release of anterior pituitary hormones, as a direct effect of interleukin-1 on the secretion of hormones. Recombinant human interleukin-1-beta was used to stimulate the secretion of hormones, including adrenocorticotropic hormone (ACTH), luteinizing (LH), growth hormone (GH), and thyroid stimulating hormone (TSH) by rat pituitary cells in a monolayer culture. Prolactin secretion was inhibited by the same concentrations (10^{-9} to 10^{-12} M) of interleukin-1 that would stimulate secretion of the other peptides. The investigators point out that the concentrations of interleukin-1 that cause secretion of pituitary hormones were similar to the range normally found in human serum; they suggest that the interleukin-1 may serve to modulate the physiological secretion of peptide hormones in vivo (Bernton et al. 1987).

Similar studies of the feedback mechanisms between interleukin-1 and glucocorticoid hormones were reported by Besedovsky and colleagues (1986). Gilmore and Weiner (1988) have shown that beta-endorphin enhances interleukin-2 production in murine lymphocytes. Other investigators have studied the interrelationships between humoral products of the immune system and both human peptide and steroid hormones. Whitcomb and colleagues (1988) have shown that human monocytes stimulate cortisol production by cultured human and adrenocortical cells. However, they could not find measurable amounts of ACTH or ACTH-like peptides released by the monocytes, perhaps because of technical limitations or because some other humoral component was

controlling cortisol release by the cultured adrenal cortex cells.

Bernton and colleagues (1988) showed that another peptide hormone, prolactin, may be important for the maintenance of lymphokyne function and also for lymphokine-dependent macrophages activation. Mice were treated with a dopamine type 2 receptor agonist, bromocriptine, which inhibits pituitary prolactin secretion by increasing dopaminergic tone. This treatment prevented T-cell dependent induction of macrophage tumoricidal activity using mice that had been infected with Mycobacterium bovis (BCG strain) or with Listeria monocytogenes, or inoculated with killed Proprionibacterium acnes. This effect of bromocriptine, presumably acting as a dopamine type 2 agonist, was observed when it was injected 1 to 3 days before inoculation with one of the bacteria. However, when this dopamine type 2 agonist was administered on day 0, that is, the same day bacteria were introduced, or on days 1, 4, and 7 after bacteria were introduced, the resultant lowering of prolactin levels did not alter macrophage activity. Concomitant treatment with exogenous ovine prolactin after lowering of endogenous prolactin levels by bromocryptine reversed this effect, with resultant normal induction of tumoricidal macrophages. The production of gamma interferon was significantly impaired in the bromocriptine pretreated animals. Lymphocyte proliferation, including both B-cell and T-cell proliferation, after stimulation with cell type specific mitogens, salmonella lipopolysaccharides and concanavalin A respectively, in vitro was also depressed in the bromocriptine-treated hypoprolactemic mice after 48 hours of bromocriptine treatment. Concomitant administration of exogenous ovine prolactin partially reversed this effect. Bernton and colleagues also showed that bromocriptine treatment increased the lethality of infectious agent challenges in mice.

Treatment of mice with cysteamine, which also suppresses pituitary secretion of prolactin, but not by action at the dopamine type 2 receptors, was shown to result in the suppression of splenic proliferative responses. This effect was also reversed by prolactin (Bernton et al. 1988). These findings suggest that it was the suppression of prolactin secretion that impaired lymphocyte responses to antigenic stimuli, by specifically reducing the production of both gamma interferon and other macrophage activating factors. The physiological and pharmacological significance of these findings is not known. However, it is well known that opiates acutely stimulate prolactin secretion and, even when opiates are administered on a chronic basis, sustained prolactin responsiveness has been described (Kreek 1978, 1987, 1989, in press).

Interesting and provocative studies have been reported over the past 3 years, including studies of the production of classical neuroendocrine hormones including ACTH by cellular elements of the immune system; the effects of humoral elements of the immune system on both central and peripheral hormone production; and the effects of two specific cytokines, interleukin-1 and interleukin-2, on enhancing the expression of the proopiomelanocortin gene, which encodes both ACTH and beta-endorphin as well as other peptide hormones in pituitary cells (Brown et al. 1987; Carr et al. 1988a,b, 1987; Harbour et al. 1987; Meyer et al. 1987; Smith et al. 1987, 1986). Some of these studies have focused on novel processing of proopiomelanocortin by mononuclear leukocytes, with resultant production of both ACTH and endorphins; the discovery of the presence of delta-subtype opioid receptors (which also have some characteristics of mu receptors) on cells of the immune system, especially on murine leukocytes; and the identification of specific ACTH receptors on human mononuclear leukocytes. A method of identifying the delta-subtype opiate receptor on cells of the immune system, including use of specific antibodies for the possible isolation and characterization of this subtype of opioid receptor, was reported by Carr and colleagues (1988a,b).

A series of studies has been conducted on the possible role of methionine enkaphalin as an immunomodulator in otherwise healthy humans. The possible therapeutic efficacy of methionine enkephalin in the improvement of immune function in the setting of AIDS, AIDS-related complex, and cancer has been

studied (Faith et al. 1987a,b; Nagy et al. 1987, 1988; Plotnikoff et al. 1987, 1988; Wybran et al. 1987). This work has included the in vitro demonstration of enhancement of natural killer cell activity in peripheral blood lymphocytes from normal volunteers and cancer patients by addition of enkephalins, and the induction of respiratory burst in human polymorphonuclear leukocytes with activation of the lipoxygenase pathway by methionine enkephalin. Nagy and colleagues (1988) found that methionine-enkephalin increased intracellular killing capability of the human polymorphonuclear leukocytes. Based on several single case studies, investigators have suggested that methionine-enkephalin, administered intravenously to human subjects in doses from 1 to 250 µg/kg by infusion, affected activation of T-cell subsets and NK cells and potentiated blastogenesis in the presence of mitogens, including phytohemagglutinin, concanavalin A, and pokeweed mitogen, as well as other stimulators of T-cell functions (Faith et al. 1987b; Nagy et al. 1987; Plotnikoff et al. 1987; Wybran et al 1987). Because the number of patients in each group studied was very small, additional studies will be needed before these findings can be considered reproducible. Their clinical importance is yet to be determined. The unexpected findings of apparent prolonged responses in human subjects after intravenous administration of this small opioid peptide-five amino acid, which has a very short half-life, because of degradation by peptidase, is not yet understood. Similarly, a prolonged activation of splenic natural killer cell activity in mice has been observed for up to 20 hours after a single injection of enkephalins. The mechanism underlying this apparent protracted response of activation of natural killer cell activity has not yet been elucidated (Faith et al. 1987b; Nagy et al. 1987; Plotnikoff et al. 1987; Wybran et al. 1987).

Other research has focused on the hypothesis that opiate addiction may be in part an immune response. Scientists have studied the effect of immunomodulators, including interferon, cyclosporine, and radiation-induced immune suppression on the morphine action of antinociception and on morphine-induced hypothermia and tolerance (Dougherty et al. 1986a,b). The possible role of lymphoid cells in opiate withdrawal symptoms in opiate-dependent rats has been studied and the opiate withdrawal system modified by administration of the immunosuppressant cyclosporine, attenuation of the opiate withdrawal syndrome by irradiation, muramyl peptides (Dafny et al. 1987, 1986; Dougherty et al. 1987a,b,c; Dougherty and Dafny 1988; Montgomery and Dafny 1987; Pellis et al. 1987) interferon, cyclophosphamide, and cortisol. These and other studies have shown that both endogenous humoral components of the immune system (e.g., interferon) and of the endocrine system (e.g., cortisol), metabolic breakdown products of bacteria cell walls (muramyl peptides), drugs known to be immunosuppressants of different types (e.g., cyclosporine A and cyclophosphamide), as well as irradiation, apparently both modulate immune function and may also simultaneously attenuate the signs and symptoms of the narcotic abstinence syndrome in animal models. All of these findings have been interpreted as suggesting that opiate dependency may involve the immune system. Opiate addiction is, therefore, in part an immune response, a hypothesis previously proposed by many different investigators but discarded and apparently disproved by most. The full physiological and, especially, pharmacological understanding of this work will depend on further studies both of the phenomena described and the mechanisms underlying these phenomena.

In one recent study, these investigators reported that interferon pretreatment 2 hours before naloxone administration precipitated narcotic withdrawal in rats dependent on morphine. It also attenuated the severity of abstinence signs and symptoms. However, such an attenuation of naloxone-induced narcotic withdrawal by interferon was not observed in rats made dependent upon methadone alone (Dougherty et al. 1987c). Although the investigators discuss the fact that the mechanisms underlying these differences have not been fully elucidated, they suggest that physical dependence upon morphine and methadone may be entirely separate phenomena involving different physiological mechanisms. Few studies would support this idea. Again, the relationship among and the

possible significance of all of these findings with respect to opiate pharmacology in addiction and in its pharmacological treatment remain to be clarified.

Other scientists have studied various aspects of the possible interrelationships among the exogenous opiates, the endogenous opioids, related peptide hormones, and immune function over the past 3 years. These studies include clinical as well as laboratory research in which human cells, animal cells, or animal models were used (Barreca et al. 1987; Brown et al. 1986; Deitch 1988; Foster and Moore 1987; Froelich 1987; Maestron et al. 1987). Each of the classes of endogenous opioids, the enkephalins, the dynorphins and the endorphins, and also each of the subtypes of the classically defined opiate receptors, including mu, delta, and kappa receptors have been implicated in the modulation of immune function. Many studies have addressed the possible interrelationships among neurological function, behavior, stress, neuroendocrine function, the endogenous opioid system, and immune function. However, in very few of these areas have firm, incontrovertible conclusions been drawn. The precise role of the exogenous and endogenous opioids on any single cellular or humoral aspect of immune function is not known (Sibinga and Goldstein 1988). Similarly, there is still considerable controversy over whether classical specific opioid receptors exist on specific cellular elements of the immune system and, if so, which subtypes of opioid receptors are formed on which specific cell types.

Controversy also persists with respect to whether cellular elements of the immune system may produce classical neuroendocrine peptides in addition to the cytokines of the immune system, and, if so, the extent of this production and its physiological and pathological relevance. Also, it is not clear whether any of the specific cytokines plays a physiological or pathological role of clinical significance in the control of production and release of central and peripheral neuropeptides and steroid hormones of the classically defined endocrine system. These questions are potentially important to understanding both the immunological effects of drug abuse and pharmacological agents used to treat drug abuse. They may also be relevant to understanding the biological basis of narcotic addiction.

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SEDATIVES AND ANTI-ANXIETY AGENTS

INTRODUCTION

Sedative and anxiolytic drugs—chemical compounds that have a calming effect and reduce anxiety—are among the most widely prescribed medications. They are used to treat anxiety, insomnia, muscle tension (spasticity), convulsions, and alcohol withdrawal. This chapter summarizes the most recent information concerning the medical and nonmedical use of such drugs, their reinforcing effects, and their ability to produce physical dependence. There are many excellent reviews of the benefits and adverse effects of these compounds (Ator and Griffiths 1987; Busto and Sellers 1986; Cole et al. 1981; Griffiths et al. 1985; Edwards 1981; Greenblatt et al. 1983; Porpora 1986), and, in particular, of the benzodiazepine compounds (Woods et al. 1987). Although their generic designations may not be familiar, their trade names, such as Equanil, Librium, Miltown, and Valium, have become

part of the popular culture. Within this class of anxiolytic/sedative drugs, the benzodiazepines are the most widely used. They have largely replaced the earlier use of barbiturates and other nonbarbiturate anxiolytic/sedatives. Because of their importance, this review focuses primarily on the benzodiazepines.

MEDICAL USE

Following the introduction of chlordiazepoxide in 1960, benzodiazepine use in the United States steadily increased, peaking at approximately 90 million annual prescriptions in 1975. About 90 percent of the anxiolytic/sedative prescriptions written during that year were for drugs of this group. Since then, the number of benzodiazepine prescriptions has declined (Food and Drug Administration (FDA) 1981, 1986). Despite this decrease, anxiolytic/sedative use remains high. Retail pharmacies dispensed 81 million benzodiazepine prescriptions in 1985. Of these, 61 million were for benzodiazepine tranquilizers and 20 million were for benzodiazepine sedatives/hypnotics (FDA 1986 (the latest available data)). Most were prescribed by physicians involved in primary care. Psychiatrists issued only 24 percent of benzodiazepine tranquilizer prescriptions and 19 percent of benzodiazepine sedative/hypnotic prescriptions. Among the benzodiazepines, alprazolam (Xanax is its trade name) was prescribed most often in 1988, ranking third highest among the top 50 prescription drugs dispensed last year (American Druggist, 1989), followed by triazolam (trade name, Halcion) ranking 17th. The use of diazepam has been steadily decreasing, now ranking 33rd (down from 19th in 1987).

Nevertheless, the trend of a decreasing number of overall anxiolytic prescriptions continues. Factors contributing to the decrease are an increased awareness of the adverse effects of chronic benzodiazepine use and increasingly negative physician attitudes toward prescribing scheduled anxiolytics/sedatives (Allgulander 1986; Balter 1987; Clinthorne et al. 1986). Though anxiolytic/sedative use continues to be common, these drugs are generally used appropriately, possibly even conservatively (Rickels 1981; Mellinger et al. 1984; Marks 1985; Woods et al. 1987). There is an increasing medical consensus that patients taking these drugs should be regularly reevaluated with a view to reducing or eliminating the drug use (Rickels et al. 1984, 1985; Higgitt et al. 1985; Owen and Tyrer 1983; Hollister 1985). New York State, for example, recently enacted a law limiting each prescription for benzodiazepines to a 30-day supply. There has also been some recent effort to limit the number of benzodiazepine compounds available on the market. Despite these changes, some inappropriate prescribing probably still occurs (FDA 1986).

NONMEDICAL USE

There are numerous well-documented reports of nonmedical use of benzodiazepines, barbiturates, and other anxiolytic/sedative drugs. It is clear from such evidence and from national surveys that these drugs are sometimes used for purposes other than accepted medical use, and that they are being sold illicitly. Accurate estimates of the extent of this nonmedical use are critical to understanding the abuse of these drugs.

Data on the nonmedical use of anxiolytics/sedatives could be approximated by the national Drug Abuse Warning Network (DAWN), sponsored by the National Institute on Drug Abuse (NIDA). The DAWN data collection system tabulates reports from emergency rooms on nonmedical drug use. These data uniquely supplement other national surveys. Drug abuse is defined by DAWN as the nonmedical use of a substance for its psychic effects, or because of dependence, or in a suicide attempt/gesture. Nonmedical uses include using prescription drugs in a manner inconsistent with accepted medical practice, taking over-the-counter drugs contrary to approved labeling, or employing any substance for its psychic effect, as a result of dependence, or in a suicide attempt.

Emergency room data from DAWN for the 3-year period from July 1984 through December 1987 show

a steady decrease in the number of emergency room mentions for all three major anxiolytic/sedative categories (tranquilizers, nonbarbiturate sedatives, and barbiturate sedatives) compared to more commonly abused drugs such as cocaine and alcohol. The greatest decline was in diazepam use (from 3,983 mentions at the beginning of the 3-year period to 3,136 at the end of the period). Diazepam is, however, still the most frequently named anxiolytic/sedative implicated in emergency room admissions and is mentioned five to six times more frequently than any other anxiolytic/sedative drug. Possibly reflecting the widespread belief that newer drugs are better, the more recently developed benzodiazepine, alprazolam, has now replaced lorazepam as the second most widely used drug in the anxiolytic/sedative class (NIDA 1988a).

Over-the-counter sleep aids are also widely misused. Although this category of drug (represented by remedies bearing such trade names as Sominex, Nitol, and Sleep-eze) is not tabulated by drug name, over-the-counter drugs are the third most frequently mentioned anxiolytic/sedative drugs in connection with emergency room admissions. Moreover, the number of emergency room mentions has not declined, despite marked decreases in the use of the other anxiolytic/sedatives.

Pharmacologically, all anxiolytic/sedative drugs are classifed as central nervous system depressants. Three classifications in the DAWN system—tranquilizers, nonbarbiturate sedatives, and barbiturate sedatives—are all central nervous system depressants. Abused drugs are taken for symptoms of somatic or psychological origin, or both (cf. Westermeyer 1987). Anxiolytics/sedatives can temporarily relieve insomnia, fear, anxiety, and restlessness. Although this may not be true of the general population, a recent survey of nonprescribed use among pharmacists and pharmacy students in one New England State showed that anxiolytic/sedative drugs were used primarily for self-treatment rather than recreational purposes (McAuliffe et al. 1987). Approximately 16 percent of emergency room mentions are for anxiolytic/sedatives. Alcohol, probably the most widely abused central nervous system depressant, is not included in that tabulation. Among the top 50 drugs mentioned in connection with emergency room admissions by the DAWN survey, 11 are from the anxiolytic/sedative class. The number of emergency room admissions resulting from the use of these drugs is higher than that of all other drug classes tabulated (the second highest is the opioid analgesic class). The top seven anxiolytic/sedative drugs, listed in descending order, are diazepam, alprazolam, over-the-counter sleep aids, lorazepam, phenobarbital, chlordiazepoxide, and flurazepam (FDA 1986; NIDA 1988a,b).

The typical nonmedical user of anxiolytic/sedative compounds is white (71.7 percent), female (approximately 60 percent), and between 20 and 40 years old (NIDA 1988a,b). When these users are admitted to the emergency room, it is usually because of an overdose (94.1 percent for over-the-counter sleep aids; 80.0 percent for other tranquilizers; 86.2 percent for nonbarbiturates; and 76.3 percent as a result of a barbiturate overdose). Thirty-seven percent of those identified by emergency room personnel as attempted suicides employed anxiolytic/sedatives, the highest mention of all those drugs listed. However, these drugs are rarely used to achieve a psychic effect or to maintain dependence, as are the other major abused compounds (cocaine, heroin/morphine, and marijuana/hashish). In marked contrast to these other drugs, anxiolytic/sedatives are usually obtained legally by prescription or from over-the-counter sources. DAWN data attribute "street buys" to only a small fraction of drug sources; however, almost half of the drug sources are classified as "unknown" (table 1).

The number of anxiolytic/sedative drug mentions in connection with emergency room treatment increases with the age of the patients (9.5 percent at ages 25 through 29; 10.5 percent between 30 and 34; 15.0 percent between 40 and 49; 21.0 percent in the 50- through 59-year-old group and approximately 33 percent when the patient was over 59). Weiss and Greenfield (1986) review prescription drug abuse from several perspectives, including that of the elderly

TABLE 1. Characteristics of Anxiolytic/Sedative Drug Class, DAWN 1987

	TRANQUILIZERS	NON-BARBITURATES	BARBITURATES
	Diazepam Alprazolam Clordiazepoxide Lorazepam Meprobamate Other/unspec	Methaqualune Flurazepam OTC sleep-aids Ethchlorvynol Glutethimide Other/unspec	Phenobarbital Secobarbital/amobarbital Secobarbital Phentobarbital Other/unspec
Used in Combination	73.3%	64.1%	71.6%
Motivation for Drug Use			
Psychic Effect	12.2%	12.5%	11.8%
Dependence	12.8%	8.2%	14.6%
Suicide	62.0%	68.0%	54.7%
Unknown	11.3%	9.6%	16.8%
Age	20-40	20-40	20-40
Drug Source			
Legal Rx	48.7%	28.4%	43.7%
Street buy	2.2%	44.4%	3.9%
Unknown	44.3%	42.0%	46.5%
Death			
Used in combination	95.5%	97.3%	85.4%
Drug-induced death	80.0%	83.6%	58.9%

population. As with other abused compounds (cocaine, heroin/ morphine, and marijuana/hashish), anxiolytic/sedatives are often used in combination with alcohol, but infrequently in combination with cocaine, heroin, and marijuana/hashish. Table 2 lists the top eight anxiolytic/ sedatives mentioned in DAWN. Diazepam is still the most frequently mentioned drug in its class, with the highest potential for misuse (FDA 1986). Emergency room admissions and deaths resulting from anxiolytic/ sedatives are common, especially when the drug involved is used in combination with other drugs. For example, all deaths involving flurazepam were due to its being used in combination with other drugs, most probably alcohol. This is important, as flurazepam is frequently prescribed for the elderly, who may be particularly vulnerable to the abuse of alcohol. Other DAWN data concerning anxiolytics/sedatives are summarized in tables 1 and 2.

Although several national surveys and the DAWN system provide valuable information about drug use among a large segment of the general population, they do not specifically provide information about anxiolytic/sedative abuse among those who abuse illicit drugs. The best current information concerning this comes from observations of those working with drug abusers in treatment and from limited surveys of drug abuse clinic clients. These sources suggest that anxiolytic/sedatives are most frequently used by those clients who are polydrug abusers (Smith and Marks 1985; Wesson and Smith 1977; Mitchelson et al.

TABLE 2. Characteristics of Anxiolytic/Sedative Drug Use, DAWN 1987

	DIAZEPAM	ALPRAZOLAM	SLEEP-AIDS	LORAZEPAM	PHENO-BARBITAL	CHLOR-DIAZEPOXIDE	FLURAZEPAM	SECO-BARBITAL
No. of Drug Mentions	7,277	3,835	1,760	1,448	1,387	1,230	1,112	213
Used in Combination	76.7%	67.3%	45.5%	70.4%	68.9%	79.8%	71.0%	77.9%
Motivation for Drug Use								
Psychic Effect	14.5%	9.9%	7.7%	11.6%	9.2%	12.3%	8.5%	12.7%
Dependence	20.4%	7.6%	0.6%	8.1%	12.3%	9.8%	4.3%	15.0%
Suicide	52.5%	71.6%	83.9%	67.0%	61.9%	66.7%	77.5%	53.1%
Unknown	11.1%	9.0%	6.0%	10.7%	14.0%	9.7%	7.4%	17.4%
Drug Source								
Legal Rx	37.6%	62.5%	11.6%	55.9%	58.6%	54.1%	58.4%	34.3%
Street buy	4.5%	0.4%	1.5%	0.8%	0.7%	1.0%	0.7%	5.6%
Unknown	52.92%	33.6%	26.0%	37.4%	37.4%	40.9%	36.2%	54.5%
Death								
Used in combination	96.8%	93.8%	---	---	84.9%	94.9%	100.0%	81.4%
Drug-induced death	81.4%	87.5%	---	---	46.4%	76.3%	79.1%	61.4%

1970). Benzodiazepines, in particular, are usually abused in combination with other drugs and are rarely listed as the primary drug of abuse (Smith and Marks 1985; Kemper et al. 1980). There is a high rate of diazepam abuse by methadone maintenance patients (Bigelow et al. 1980; Budd et al. 1979; Hargreaves et al. 1983; Hartog and Tusel 1987; Woody et al. 1975 a,b; Kaul and Davidow 1981; Stitzer et al. 1981). However, the proportion of users varies markedly by clinic, ranging from as low as 4 percent to as high as 65 percent, although it is relatively constant within individual clinics. The interclinic variation may be due to differences in clients' social class, culture, age, and ethnicity. Ten to thirty percent of methadone maintenance clients used diazepam concurrently with methadone. Diazepam users in this group tend to use other drugs as well (Woody et al. 1975a), but persons addicted to diazepam rarely switch to other benzodiazepines because the others seem to lack any euphoric effects (Kleber and Gold 1984). There is an unconfirmed belief among drug addicts that the combination of diazepam and methadone has a heroin-like euphoric effect. A double-blind clinical pharmacologic study found that diazepam enhances some of the subjective and physiological opioid effects in methadone maintenance patients, concurrently producing sedative-like subjective effects (Preston et al. 1984). Hartog and Tusel (1987) reported that use and abuse of anxiolytic/sedatives or alcohol by methadone maintenance clients could be classified into two categories, one representing general addictiveness, the other involving the use and abuse of nonopiates in an attempt at self-medication. Methadone maintenance clients may use diazepam for anxiety, dysphoria, or other symptoms resulting from their other drug abuse. Hartog and Tusel (1987) found that diazepam users were significantly more disturbed psychiatrically than nonusers. Alcoholics also appear to be at high risk of abusing benzodiazepines (Busto et al. 1983; Wiseman and Spencer-Peet 1985), in particular, alprazolam, to alleviate discomfort (Ciraulo et al. 1988). Caffeine-induced anxiety-like symptoms can be antagonized by diazepam (Roache and Griffiths 1987), and a greater use of benzodiazepines has been reported among heavy caffeine drinkers than among low to moderate caffeine users (Greden et al. 1978, 1981; Proctor and Greden 1982).

ABUSE LIABILITY

One problem with the use of chemicals or drugs that alter mood and feeling is the tendency for some individuals to develop a dependence on these compounds. Such individuals continue to take the substances in the absence of medical indications, despite their adverse medical and social consequences, and behave as if the drugs' effects are essential to their continued well-being. If the substance used is inexpensive and not very toxic, dependence on it may not cause a significant medical or social problem. More commonly, however, compulsive drug use has deleterious effects for both the user and the society. Although the problem of drug use or abuse is often related to the drug itself, or to the person who has the problem, or to the society, this type of analysis tends to oversimplify the problem. Westermeyer (1987) summarized drug abuse and alcoholism problems in terms of the interactions of the host (person), the drug(s), and the environment. Use of this public health model is one way of understanding the complex nature, extent, spread, patterns, and associated aspects of drug abuse. (This chapter focuses on the psychopharmacological aspect of this specific drug class, primarily the host-drug interaction, as other chapters deal with other aspects of the overall drug problem.)

Two major characteristics of a substance that has abuse liability are its reinforcing properties (the capacity to maintain self-administration of the substance) and its adverse effects (the harm it causes the individual, the society, or both) (cf. Brady 1988; Woods et al. 1987). Anxiolytic/ sedatives have both of these characteristics.

Abuse Liability in Humans

One way of characterizing the abuse liability of a drug is to conduct a placebo-controlled, double-blind experiment in order to investigate the drug's behavior-reinforcing and subjective properties, using as subjects people with and without histories of drug abuse (Griffiths and Roache 1985). In this type of experiment, the experimental drug is compared with a substance that resembles it but is chemically inert (inactive). Neither the experimenter nor the subjects know which drug has been given until the experiment is completed (the "double-blind" condition). Such a design prevents the experiment from being systematically influenced by the expectations of the participants. The reinforcing effects of the drug are assessed by various drug self-administration conditions; its subjective effects (e.g., producing a euphoric feeling) are measured by rating scales. Measuring only the drug's subjective effects, however, is not adequate to determine its reinforcing properties (cf. Woods et al. 1987). De Wit and Johanson (1987) and Brady (1988) have reviewed the problems associated with using human subjects in such assessments, including those associated with drug preference testing and with measuring subjective effects in general.

In human studies comparing the reinforcing and subjective effects of benzodiazepines (diazepam, chlordiazepoxide, or triazolam) with those of a barbiturate (pentobarbital), using subjects with a history of drug abuse, the barbiturate has been generally shown to have a greater abuse liability. These results are consistent with studies in which animals self-administer the drugs (Griffiths and Roache 1985).

The benzodiazepines have reinforcing effects (tend to maintain self-adminstration), produce subjective "liking" effects, or both. This indicates their potential to be abused. This conclusion is based on placebo-controlled, double-blind experiments using subjects with a history of drug abuse (Griffiths and Roache 1985). Although the magnitude of these effects varied, all of the benzodiazepines tested (diazepam, triazolam, oxazepam, prazepam, halazepam, lorazepam, and chlordiazepoxide) were found to have reinforcing or subjective "liking" properties, or both. Relatively high doses of these benzodiazepines were selected; they have different pharmacokinetic profiles (that is, they have a fast versus slow onset of action, fast versus slow rate of elimination, or both), and they represent compounds used for different medical purposes (e.g., anxiety-reducing drugs versus sleep-inducing or hypnotic compounds). However, Healy and Pickens (1983) examined subjects' preference for diazepam doses falling within the recommended therapeutic range and found no preference for any of the doses tested. These results indicate the pharmacological importance of dose ranges. It is noteworthy that diazepam and the other benzodiazepines tested were not found to be effective reinforcers in normal human subjects who had never abused drugs (Johanson and Uhlenhuth 1980; de Wit et al. 1984a,b, 1986). In a series of studies using a double-blind choice procedure, a majority of subjects who were not drug abusers not only did not show a preference for benzodiazepines in doses high enough to produce appreciable subjective responses, but avoided them altogether. Similar results were obtained with some high-risk subjects who might be expected to use these drugs in excess. For example, de Wit et al. (1986) reported that highly anxious subjects, who were expected to prefer diazepam because of its anxiety-reducing properties, chose the placebo instead. Although benzodiazepines have positive reinforcing and subjective "liking" properties in individuals who have abused drugs in the past, this does not appear to be true in subjects who have not abused drugs. However, a more recent report by de Wit et al. (1989), raises an important issue in the labeling of an individual as a "drug abuser," and/or in identifying a segment of the population as being vulnerable to drug abuse.

Their studies on normal healthy volunteers with histories of light to moderate social alcohol use show that benzodiazepine (diazepam) was clearly reinforcing when self-administered. The important issue to emerge from these studies is that although the subjects may not be labeled as "alcoholic," and the resulting

alcohol effects may be subclinical, the light and/or moderate dose of alcohol consumption in some way affected the central nervous system, causing the benzodiazepines to clearly be reinforcing.

Several studies comparing the reinforcing and subjective effects of different benzodiazepines have found differences among them. Specifically, lorazepam appears to produce reinforcing and subjective effects similar to those of diazepam, whereas oxazepam, halazepam, chlordiazepoxide, and triazolam may have a lower abuse potential than diazepam (Griffiths and Roache 1985; Roache and Griffiths 1986). The most thorough comparison has been between diazepam and oxazepam (Griffiths et al. 1984b). When these two drugs were compared over a wide range of doses (10 to 160 mg diazepam; 30 to 480 mg oxazepam), diazepam was found to have the greater abuse liability (Bergman and Griffiths 1986). The effects of diazepam had a more rapid onset than did those of oxazepam, an effect that was critical and was repeatedly cited as desirable by subjects. Behavioral choice tests showed that diazepam was a more effective reinforcer than oxazepam. The conclusion that diazepam and lorazepam have a greater abuse liability than oxazepam has been epidemiologically confirmed in subsequent analyses of drug abuse data from the United States and Sweden (Griffiths et al. 1984b; Roache and Griffiths 1987). Alprazolam seems to be equivalent to lorazepam in producing these effects. The differences in the reinforcing and subjective effects among the benzodiazepines are analogous to those found with barbiturates. Phenobarbital, which has a slower onset of action and is longer acting, is not as well "liked" and produces less euphoria than pentobarbital or secobarbital (Fraser and Jasinski 1977; Wesson and Smith 1977). This is consistent with the clinical observation that there is a very low incidence of abuse of phenobarbital, as characterized by drug-seeking behavior, compared to the other barbiturates (Fraser and Jasinski 1977).

A more recently developed anxiolytic, buspirone, is a nonbenzodiazepine drug. Buspirone has been shown in clinical trials to be equally effective to more commonly used benzodiazepines in treating generalized anxiety disorder (Feighner et al. 1982; Goldberg and Finnerty 1979; Rickels et al. 1982; Ross and Matas 1987) and has minimal sedative properties (Cohn and Wilcox 1986). Data from both animal (Balster and Woolverton 1982; Riblet et al. 1982; Hendry et al. 1983) and human studies (Cole et al. 1982; Griffiths et al. 1986) indicate that buspirone has little, if any, abuse liability compared to the benzodiazepines. This experimental prediction seems to hold true epidemiologically as well. No abuse cases involving buspirone have been noted in the medical literature in the past 3 years.

Reinforcing Effects in Animals

The human tendency to take certain chemicals and drugs is shared by other mammals. Laboratory animals quickly learn to self-administer the drugs often used for nonmedical purposes by people. Furthermore, the rank order of drugs abused by humans is similar to that found when animals are permitted to self-administer these substances (Brady et al. 1975; Johanson and Balster 1978; Griffiths and Balster 1979). These animal observations suggest that preexisting psychopathology is not a prerequisite for initial or even continued drug-taking behavior, and that drugs in themselves can be powerful reinforcers (Griffiths et al. 1980; Johanson and Schuster 1981).

Drug self-administration studies using laboratory animals have contributed much valuable information about the reinforcing effects of chemicals in humans. Drug self-administration procedures in laboratory animals permit assessment of the likelihood that these drugs will be abused by people. These experiments provide early warnings that particular drugs have the potential to be abused. The validity of this approach is indicated by the fact that drugs that laboratory animals will self-administer are also abused by humans, produce profiles of animal response that are predictive of human abuse, or have both of these characteristics (Griffiths and Balster 1979; Griffiths et al. 1980). Numerous studies have shown (cf. Griffiths

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and Ator 1981; Yanagita et al. 1981; Griffiths et al. 1985) that the benzodiazepines are less effective as reinforcers than barbiturates such as pentobarbital, amobarbital, secobarbital, or psychomotor stimulants such as cocaine. Among the benzodiazepines, triazolam and midazolam, which are rapidly eliminated in humans, maintain higher levels of self-injection than benzodiazepines that are more slowly eliminated (Griffiths et al. 1981, 1985). Triazolam and midazolam, however, do not maintain the consistently high levels of self-injection found with most barbiturates. The reinforcing effects of diazepam are blocked by the benzodiazepine receptor antagonist RO15-1788 (Johanson and Schuster 1986).

TOLERANCE AND PHYSICAL DEPENDENCE

Chronic intoxication with short-acting barbiturates and related hypnotics results in changes in both drug-disposition and central nervous system adaptation (i.e., pharmacodynamic tolerance). Pharmacodynamic tolerance can also develop to most of the actions of benzodiazepines, but drug-dispositional tolerance is less marked. The slow accumulation of long-acting active metabolites of many benzodiazepines may undermine the measurement of adaptive changes occurring in the central nervous system. In general, the benzodiazepines are considerably safer than barbiturates and related sedatives, because an acute overdose is less likely to produce fatal respiratory depression. However, one of the general characteristics of central nervous system adaptation to anxiolytic/sedative drugs, including alcohol, is that considerable tolerance develops to their sedative and intoxicating effects, but the lethal dose is not markedly changed by chronic use (Okamoto et al. 1978). Consequently, acute anxiolytic/sedative poisoning can occur at any time, most commonly after alcohol consumption, especially because the absorptive and depressant actions of anxiolytic/sedatives are also increased when alcohol is consumed. This can lead to life-endangering central nervous system depression. This combined depressant effect on the central nervous system is more than simply additive (Okamoto et al. 1986) and is reflected in DAWN statistics on the frequency of emergency room fatalities produced when these drugs are used in combination, especially with alcohol.

All anxiolytic/sedative drugs produce physical dependence. Physical dependence is an adaptive state resulting from chronic exposure to a substance, but it becomes apparent only when this chronic exposure is abruptly ended and a characteristic set of symptoms called a withdrawal syndrome occurs.

The withdrawal symptoms represent a kind of rebound effect in the same physiological systems that were initially modified by the drug's use. A drug's ability to produce physical dependence does not inevitably lead to abuse of that drug. For example, among the anxiolytic/sedative drugs, phenobarbital produces physical dependence, but does not usually lead to drug-seeking behavior (Fraser and Jasinski 1977). However, the desire to relieve adverse withdrawal effects resulting from physical dependence may reinforce drug-seeking behavior.

There are marked similarities in the withdrawal syndromes seen with all anxiolytic/sedatives, including barbiturates, meprobamate, glutethimide, methaqualone, benzodiazepines, and related drugs. The term "general central nervous system depressant withdrawal syndrome" is therefore used to refer to the withdrawal syndrome produced by all of these drugs. Among the most severe signs of anxiolytic/sedative withdrawal, including withdrawal from alcohol, are delirium and grand mal convulsions. Life-threatening grand mal convulsions are more likely to occur in this type of withdrawal than when opioids are discontinued, necessitating medical attention when anxiolytic/sedatives are withdrawn.

Physical Dependence in Animals

Most of the information about physical dependence on drugs has come from animal and human studies of chronic opioid, barbiturate, and ethanol (that is, beverage alcohol) administration and withdrawal. These traditional drugs of abuse have served as prototypes for characterizing and assessing the physical dependence liability of newer compounds suspected of having abuse potential.

Three procedures are used to study physical dependence in animals. These are spontaneous withdrawal tests, in which the animals are chronically given a test drug, the drug is then abruptly withdrawn, and signs of withdrawal are assessed; cross-dependence tests, in which the ability of a test drug to suppress withdrawal signs from another abused drug is measured; and precipitated withdrawal tests, in which a specific receptor antagonist (a chemical that blocks or reverses the action of the test drug) is used to precipitate withdrawal in animals made physically dependent on the test drug.

Studies in animals have clearly shown that physical dependence on barbiturates and benzodiazepines is a function of dose and duration of chronic drug administration (Fraser and Jasinski 1977; Okamoto 1984; Lukas and Griffiths 1984; Rosenberg and Chiu 1985). The extent of chronic nervous system drug exposure is important for the development of tolerance and physical dependence. The severity of the withdrawal reaction reflects the speed of disappearance of the sedatives from the plasma, which in turn reflects their disappearance from their sites of action in the nervous system. The more slowly a drug is eliminated from the body, the milder the withdrawal; the faster it is eliminated, the more severe the withdrawal (Okamoto 1984). These basic facts hold true when two drugs in the same class that have different pharmacokinetics are compared, as shown in a series of barbiturate experiments (Boisse and Okamoto 1978). But they are also true when two individuals with different rates of elimination of the same drug are compared (Okamoto et al. 1986). This finding probably reflects the limited rate of re-adaptation of the central nervous system to the removal of the drug. To date, a similar phenomenon has not been clearly shown in spontaneous withdrawal studies with the benzodiazepines (Griffiths et al. 1985; Woods et al. 1987). Although many studies have quantitatively assessed the intensity of withdrawal signs correlated to the elimination rates of the drugs, those differences in elimination kinetics have not been taken into consideration during chronic treatment procedures. In this respect, it is interesting to note that the manifestation and characteristics of the withdrawal from diazepam depend on its slowly eliminated metabolite, nordiazepam, rather than diazepam itself (McNicholas et al. 1988).

Only a few studies have systematically examined the physical dependence potential of benzodiazepines over wide dose ranges that include low doses relevant to their therapeutic use. However, numerous animal studies have shown that at high doses, all benzodiazepines can produce physical dependence. There have been reports that the withdrawal signs may be slightly different with different benzodiazepines (McNicholas et al. 1983, 1985; Stockhaus 1986, Martin et al. 1989). However, the relative significance of the various benzodiazepines has not been well established.

Benzodiazepines generally suppress barbiturate withdrawal in drug substitution procedures (Fraser and Jasinski 1977; Woods et al. 1987; Yanagita 1981). However, several substitution studies suggest that cross-dependence between barbiturates and benzodiazepines may not be complete (Griffiths et al. 1985; Martin et al. 1982).

Studies of benzodiazepine-precipitated withdrawal using an antagonist of benzodiazepine (e.g., flumazenil—RO15-1788, CGS-8216) have revealed a remarkable quickness, susceptibility, or both of adaptive processes of the central nervous system to benzodiazepine. This benzodiazepine antagonist precipitated withdrawal signs in several animal species (baboons, squirrel monkeys, dogs, cats, and rats) after high/low doses of diazepam, triazolam,

lorazepam, or flurazepam (Cumin et al. 1982; Lamb and Griffiths 1984, 1987; Lukas and Griffiths 1982; McNicholas and Martin 1982, 1986; McNicholas et al. 1983) even after only 1 to 3 days of exposure to higher benzodiazepine doses (Lukas and Griffiths 1984; Rosenberg and Chiu 1985). Martin et al. (1989) have compared flumazemil-precipitated withdrawal signs in dogs after making them dependent on diazepam, nordiazepam, flunitrazepam, alprazolam, oxazepam, halozapam and lorazepam. The precipitated abstinence signs were very different among the different benzodiazepines, including their metabolites. Diazepam and flunitrazepam produced withdrawal signs characterized not only by high incidences of clonic convulsions, but also by a high "Diazepam-Precipitated Abstinence" type score, while nordiazepam and alprazolam produced relatively low "Diazepam-Precipitated Abstinence" scores, with similar incidence of clonic convulsion.

Since different species metabolize benzodiazepines differently, the type of physical dependence produced may differ among different species. Furthermore, the metabolism of benzodiazepines plays an important role in their capacity to produce dependency. Other studies have shown that interpretation of these findings is not simple (Giorgi et al. 1988), and quantitative comparison of signs due to simple drug withdrawal with those following different types of antagonist administration must continue.

Physical Dependence in Humans

Chronic use of anxiolytic/sedative drugs by humans can also lead to physical dependence. The signs and symptoms associated with discontinuing chronic use include anxiety, insomnia, agitation, anorexia, tremor, muscle twitching, nausea, vomiting, hypersensitivity to sensory stimuli and other perceptual disturbances, depersonalization, hallucinations, delirium, grand mal convulsions, and occasionally death (Isbell et al. 1950; Fraser and Jasinski 1987; Marks 1985; Schopf 1983). The more severe withdrawal signs and symptoms usually occur only after prolonged exposure to high doses.

The withdrawal syndrome following termination of short-acting barbiturates commonly used as hypnotics (i.e., pentobarbital, secobarbital, and amobarbital) and alcohol has been characterized in a series of nonblind experiments in subjects with and without histories of drug abuse (Isbell et al. 1950; Fraser et al. 1958; Fraser and Jasinski 1977). Following a gradual recovery from intoxication over 6 to 15 hours, patients start to show minor withdrawal signs and symptoms, which, in those who have used heavily, are often followed over the course of 24 hours or more by grand mal convulsions, auditory or visual hallucinations, and delirium. The severity of withdrawal symptoms and the incidence of grand mal convulsions depended on the size of the chronically administered doses. Furthermore, a rapidly eliminated barbiturate produced more severe withdrawal symptoms than a slowly eliminated barbiturate (Wulff 1959). Severe withdrawal reactions (i.e., seizures and psychoses) have also been reported following abrupt termination of high doses of such nonbarbiturate sedatives as meprobamate, glutethimide, ethinamate, ethchlorvynol, and methprylon (Essig 1966).

The animal and human data available have not yet provided a basis for differentiating the physical dependence characteristics of the various benzodiazepines and other anxiolytic/sedatives. Most of the signs and symptoms that have been described for pentobarbital and secobarbital withdrawal have also been noted in studies or case reports of benzodiazepine withdrawal. A major difference has been that severe withdrawal signs such as seizure and delirium are less common during benzodiazepine withdrawal. However, because most of these high-dose benzodiazepine studies and reports have involved benzodiazepines that either are slowly eliminated or have active metabolites that are slowly eliminated, it is not clear whether the differences in withdrawal severity between drugs such as diazepam and pentobarbital represent inherent pharmacodynamic differences or simply reflect differences in the drugs'

rate of elimination from the body (pharmacokinetic differences).

The high-dose benzodiazepine withdrawal syndrome has been experimentally studied. Hollister and coworkers (1961) abruptly switched 11 psychiatric patients to placebo after 2 to 6 months of high daily doses of chlordiazepoxide (8 to 20 times the usual therapeutic dose). Withdrawal signs occurred in 90 percent of patients between 2 and 8 days after drug termination. These symptoms included depression, aggravation of psychoses, agitation, insomnia, loss of appetite, and nausea; two patients had grand mal convulsions on days 7 and 8. Subsequent studies and clinical observation have confirmed these findings and extended them to other benzodiazepines (Hollister et al. 1963; Petursson and Lader 1981a), including studies in which patients have taken high doses of diazepam for 3 to 14 years (Mellor and Jain 1982).

It is now clear that benzodiazepines can produce physical dependence after prolonged treatment, even at normal therapeutic doses (cf. Winokur et al. 1980; Owen and Tyrer 1983; Schopf 1983; Lader and Petursson 1984b; Woods et al. 1987; Busto et al. 1986). The profile, intensity, and time course of signs and symptoms following termination of drug administration enable the clinician to differentiate true pharmacological withdrawal from the reemergence of preexisting clinical symptoms. Although the most severe withdrawal signs (seizures and delirium) are generally absent in therapeutic dose dependence, other minor withdrawal signs and symptoms can occur. These include anxiety, insomnia, irritability, tremor, muscle twitching, headache, gastrointestinal disturbance, feelings of depersonalization, and various perceptual changes such as paresthesis and hypersensitivity to light and noise (Schopf 1983). Because most therapeutic dose withdrawal studies have focused on benzodiazepines rather than on barbiturates, it is not clear whether the profile of subtle withdrawal signs and symptoms differs between these two drug classes. It is known that barbiturate withdrawal often is associated with a variety of subtle perceptual changes (Fraser et al. 1958; Epstein 1980) that may be similar to those described during benzodiazepine withdrawal.

Onset of withdrawal from benzodiazepines takes from 1 to 10 days after abrupt cessation (Owen and Tyrer 1983). Estimates of the persistence of therapeutic dose withdrawal have varied from 5 days (Owen and Tyrer 1983) to 6 months or longer of protracted withdrawal syndromes (Higgitt et al. 1985; Ashton 1984). This variation could be due to variations in patients' subjective reports and in systems for the clinical evaluation of withdrawal symptoms. However, in studies of relatively unselected patient groups, nearly half (45 percent) of these patients experienced withdrawal after long-term benzodiazepine use even when the drug was withdrawn gradually (Tyrer et al. 1981, 1983). The minimum duration of benzodiazepine treatment necessary to produce significant therapeutic dose dependence is unclear and controversial. It has been estimated to be as short as 4 to 6 weeks (Fontaine et al. 1984; Power et al. 1985; Murphy et al. 1984) and as long as 8 months (Rickels et al. 1983). When rebound insomnia (a worsening of sleep after treatment with hypnotic drugs) has been included as one sign of drug withdrawal, dependence has been reported after only 2 weeks of benzodiazepine use (Kales et al. 1985; Bixler et al. 1985).

As with nonbenzodiazepine anxiolytic/sedatives, withdrawal severity and latency to onset of withdrawal seem to be related to the speed of drug elimination. With rapidly eliminated benzodiazepines (e.g., lorazepam, triazolam), withdrawal symptoms occur sooner than with the more slowly eliminated compounds or those with slowly eliminated metabolites (e.g., diazepam, flurazepam) (Tyrer et al. 1981; Tyrer and Scivewright 1984; Griffiths et al. 1985; cf. Tyrer and Murphy 1987). Also, the incidence and intensity of the withdrawal signs and symptoms are greater with the rapidly eliminated compounds than with the more slowly eliminated ones (Walters and Nel 1981; Fontaine et al. 1984). In this respect, there are many anecdotal reports (Consumers' Association 1987) and one study (Tyrer et al. 1981) that suggest that lorazepam is at particular risk of producing depend-

ence. Lorazepam is a fairly potent benzodiazepine with an equivalent half-life to oxazepam (Griffiths et al. 1984). More recently, alprazolam, a benzodiazepine of similar potency and half-life to lorazepam, has also acquired a reputation for posing a greater risk of dependence than the other benzodiazepines used in the United States (Browne and Hauge 1986; Kantor 1986; Slak 1986).

Drug rebound insomnia, which might occur during withdrawal, is one of the important adverse effects of anxiolytic/sedative-hypnotic medication. It may reinforce drug-seeking behavior. Rebound insomnia has been reported with benzodiazepines (Kales et al. 1985). By analogy to barbiturate dependence, it has been hypothesized that benzodiazepine withdrawal severity should be greater for the compound that leaves the brain more rapidly (Hollister 1981) (assuming an equivalent level of physical dependence to the two benzodiazepines being compared). Although this inverse relationship between benzodiazepine plasma level and severity of withdrawal symptoms has been found in some studies (Tyrer et al. 1981; Kales et al. 1986), others have failed to confirm it (Ashton 1984; Tyrer et al. 1983; Mitler et al. 1984; Rhodes and Rhodes 1984). A well-controlled experimental study supports the hypothesis. It showed that in self-referred patient groups undergoing abrupt benzodiazepine detoxification, the severity of early withdrawal symptoms and the dropout rate were higher with the quickly eliminated lorazepam than with diazepam, which has a slowly eliminated metabolite (Jochemsen and Bremier 1984). There may also be some intrinsic differences in the ability of the benzodiazepines to produce physical dependence independent of pharmacokinetic factors. A more recent report (Bixler et al. 1987) analyzed adverse reactions to benzodiazepine hypnotics (i.e., flurazepam, temazepam, and triazolam), through the Spontaneous Reporting System (SRS) of the FDA. In general, triazolam, the shortest acting among the three, had the highest overall rate of adverse reactions as reported by the SRS, hyperexcitability and withdrawal, and flurazepam, which has the most slowly eliminated metabolite, had the least effect. Amnesia and other cognitive, as well as affective effects, were also much greater for triazolam than for the other two.

The risks of withdrawal from buspirone following long-term treatment have also been compared with those of the benzodiazepines (Rickels et al. 1988). Patients were treated with therapeutic doses of buspirone for 6 months, then the drug was withdrawn. In agreement with many other studies (Fontaine et al. 1987; Olajide and Lader 1987), the buspirone-treated patients did not show any withdrawal symptoms; on the other hand, a higher dropout rate in buspirone-treated patients raised questions about patient satisfaction with therapy in a chronically anxious population (Olajide and Lader 1987; Lader and Olajide 1987).

BENZODIAZEPINE RECEPTORS

Molecular studies of drug and neurotransmitter receptors have advanced our understanding of synaptic events in the brain, of the actions of hormones, and the mechanisms of therapeutic and adverse effects of numerous classes of drugs. Receptors which mediate the pharmacologic actions of benzodiazepines were identified by binding studies utilizing tritiated diazepam bound to brain membrane. These studies have shown that at the brain receptors, benzodiazepine does not compete with gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, but rather that low concentrations of GABA stimulates the receptors to enhance their affinity for the benzodiazepine. The overwhelming body of evidence now indicates that the benzodiazepine receptor is a separate recognition site on the GABA receptor, being distinctly different from the GABA recognition site. A single protein complex of GABA receptor incorporates the chloride ion channel along with separate, but interactive, recognition sites for GABA, the benzodiazepines, barbiturates and meprobamate (and also, possibly ethanol) (cf. Snyder, 1989).

In studies using the purified GABA-benzodiazepine receptor, barbiturates, meprobamate, and

ethanol interact with the receptor at sites distinct from the benzodiazepine and GABA recognition sites. Molecular cloning of the GABA-benzodiazepine receptor and expression of the cloned protein have clarified how GABA acts as an inhibitory neurotransmitter (Schofield et al. 1987). Gamma-aminobutyric acid is known to hyperpolarize neurons by opening chloride ion channels, thereby inhibiting depolarization caused by excitatory stimuli. Molecular cloning studies reveal that a single protein contains both the GABA and drug recognition sites, as well as the chloride ion channel.

Another line of interesting studies has revealed that there are two distinct subtypes of benzodiazepine receptor. One is the "central" receptor, occurring exclusively in the brain and spinal cord, while the other is a "peripheral" one, being abundant in various glands, in particular the adrenal cortex. While diazepam has similar binding characteristics at the central and peripheral receptors, other benzodiazepines, such as clonazepam (one of the most potent benzodiazepines for producing behavioral responses), has a few thousand times weaker binding affinity at the peripheral than central sites. On the other hand, RO5-4864, a benzodiazepine devoid of anti-anxiety effects, is several thousand times more potent at the peripheral receptors than at the central ones (cf. Snyder, 1989). Characterization of these subtypes of benzodiazepine receptors, and the development of "central" and/or "peripheral" receptor-selective compounds, are important advances with potential clinical implications.

At therapeutic blood levels of diazepam, the peripheral receptors should be fully occupied and presumably influence glandular functions. Benzodiazepine is known to alter the secretion of several pituitary hormones (Grandison, 1983). These effects most likely represent the direct influence of benzodiazepine on the peripheral-type benzodiazepine receptors.

In the brain, peripheral benzodiazepine receptors are demonstrable in selected areas such as the olfactory neurons, the choroid plexus, and glial cells. A striking increase in receptor density occurs in proliferating glial cells of glial brain tumors. The extraordinary increase in these receptors in glioblastoma may permit their imaging by positron emission tomography using benzodiazepine probes (Starosta-Rubinstein et al. 1987).

Subcellular fractionation studies reveal that within cells, the peripheral receptors occur almost exclusively in mitochondria, specifically in association with the outer membrane of the mitochondria. The outer membrane of mitochondria regulates the ingress and engress of mitochondrial metabolites, a quite conceivable role for the receptors. Binding studies of radioligands to the mitochondrial (peripheral-type) receptor show that naturally-occurring porphyrins, such as heme, are the endogenous ligands of the peripheral receptors. The porphyrin-receptor association may play important physiological roles, such as affecting mitochondrial respiration. Also, the different porphyrins vary markedly in their affinities for the receptor, with the most strongly binding porphyrins (ex., protoporphyrin IX) being those with known physiological activity (Verma et al. 1987).

SUMMARY

Benzodiazepines are the safest, most effective, and most widely prescribed anxiolytic/sedatives currently available. Over the past 2 decades they have largely replaced barbiturates and other anxiolytic/sedative drugs that were in widespread earlier use. The nonmedical use (i.e., abuse) of barbiturates and benzodiazepines (especially diazepam) has decreased steadily in recent years. Clinical observation suggests that most of the emergency room overdose cases involving anxiolytic/sedatives arose when they were used in combination with other abused drugs, most often alcohol. In the illicit drug culture, these drugs are most often used by polydrug abusers; however, the number of illicit anxiolytic/sedative users is not large compared to users of other drugs of abuse. Although the number of diazepam users has declined, it is still a widely used and misused benzodiazepine.

Alprazolam also became a highly abused drug, replacing lorazepam in the number of DAWN mentions; misuse of over-the-counter sleep aids is common and persistent. Illicit use of diazepam-opioid combinations is also common. Individuals may self-medicate so as to reduce or eliminate the dysphoric effects of their opioid use.

Experiments in laboratory animals have shown that all benzodiazepines have reinforcing properties. However, they are clearly less effective reinforcers than barbiturates with intermediate half-lives, such as pentobarbital, or than psychomotor stimulants such as cocaine. Analogous studies in humans have confirmed that the reinforcing and subjective effects of benzodiazepines are less than those of pentobarbital. In addition, human studies suggest that the reinforcing and subjective effects of lorazepam are similar to those of diazepam, whereas the reinforcing and subjective effects of diazepam are greater than those of the other benzodiazepines, including oxazepam.

Studies in laboratory animals and humans have shown that abrupt termination of high chronic doses of barbiturates and benzodiazepines can produce a severe withdrawal syndrome sometimes including delirium and grand mal convulsions. It is now clear that benzodiazepines, even with normal therapeutic doses, can produce a withdrawal syndrome after long-term treatment. In general, the severity of withdrawal is related to the kinetics of drug elimination; the faster the elimination, the more severe the withdrawal. The relatively new anxiolytic, buspirone, seems as effective as the other benzodiazepines for the treatment of generalized anxiety disorder and does not seem to pose an abuse potential. However, the fact that buspirone has a different mode of action and is not cross- dependent with the benzodiazepines means that it may not be equally acceptable to patients accustomed to taking a benzodiazepine.

Although additional research is needed to determine the risk/benefit ratio of long-term benzodiazepine use, there is an increasing clinical consensus that chronic maintenance of patients on anxiolytics is not desirable, and such patients should be regularly reevaluated.

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NICOTINE DEPENDENCE

INTRODUCTION

In the 1970s and early 1980s, the biological basis for tobacco use and the dependence-producing effects of nicotine were a major focus of National Institute on Drug Abuse (NIDA) researchers, who studied the reinforcing and physical dependence-producing effects of nicotine as well as better methods for treating nicotine dependence. Much of this work has been documented in the First and Second Triennial Reports, in NIDA research monographs (Jarvik et al. 1977; Krasnegor 1978, 1979a,b,c; Grabowski and Bell 1983; Grabowski and Hall 1985a), and in Surgeon General C. Everett Koop's 1988 report, *The Health Consequences of Tobacco Use: Nicotine Addiction* (Office on Smoking and Health (OSH) 1988). Research conducted by scientists within NIDA and by other NIDA-supported investigations provided much of the critical new literature reviewed in the Surgeon General's report and

led to several of the conclusions shown in table 1. This chapter summarizes research findings published since the Second Triennial Report and emphasizes NIDA-supported research aimed at better understanding, preventing, and treating nicotine dependence.

THE ROLE OF TOBACCO USE IN OTHER FORMS OF SUBSTANCE ABUSE

It is increasingly clear that tobacco use is involved in the initiation of other psychoactive drug use and that smoking levels are often related to the use of other abusable drugs. One of the strongest findings illustrated by data from the National Household Survey (table 2) is the striking relationship between cigarette smoking and the use of alcohol, cocaine, and marijuana. The use of smokeless tobacco is also associated with that of illicit drugs. Individuals who increased their use of smokeless tobacco over a 9-month period also increased the likelihood of their using an illicit drug or increasing their use of illicit drugs already tried (Ary et al. 1987). Similarly, a study of cigarette smoking and drinking in 7th through 12th grade students found a positive correlation between their frequency of alcohol use and both their probability and frequency of cigarette smoking (Welte and Barnes 1987). An analogous finding in adults is that the number of cigarettes smoked per day is related to the severity of alcoholism, as measured by the Michigan Alcoholism Screening Test (MAST) and "habit strength" scales (Kozlowski et al. 1984; Henningfield, Clayton, and Pollin, in press).

THE EFFECTS OF PRENATAL NICOTINE EXPOSURE ON DEVELOPMENT

When tobacco is smoked, the nicotine it contains is rapidly distributed to all parts of the body. In a pregnant woman this can result in exposure of the fetus to substantial levels of nicotine (Luck and Nau 1987; Nash and Persaud 1988; Navarro et al. 1988; OSH 1988). Some of the effects of maternal cigarette smoking have been well documented. They include diminished average birth weight, more frequent miscarriages, and other birth-related problems (OSH 1988). It is possible that the fetus may also become physically dependent on nicotine and that prenatal nicotine exposure may be a risk factor for later development of tobacco and other psychoactive substance dependency, but no studies on these effects have been reported. However, additional consequences of prenatal cigarette smoking have been studied by NIDA researchers and are summarized below.

Fried and colleagues conducted an extensive series of studies on the effects of children's prenatal exposure to tobacco, alcohol, marijuana, and other drug use on physical, neurological, and behavioral development. One study (Fried and O'Connell 1987) measured birth size and subsequent growth rates as a function of substance use by the mother just before pregnancy and during the first and third trimesters, as well as average use during pregnancy. Nicotine had the most pronounced effect of the drugs studied. After other possible factors were taken into account, nicotine use prior to and during pregnancy resulted in lower birth weight and reduced head circumference at birth. Other studies have found prenatal cigarette exposure to be associated with increased tremors, poor auditory habituation, hypertonicity, and increased nervous system excitation lasting at least a month after birth (Fried and Makin 1987; Fried et al. 1987). Lower developmental scores at 1 year of age and altered auditory responses at 1 and 2 years of age were also reported (Fried and Watkinson 1988). The Fried and Watkinson study also found that postnatal environmental factors complicated efforts to determine if prenatal maternal cigarette smoking was the specific cause of cognitive deficiencies in the abilities of 2-year-olds.

Another series of studies of the effects of prenatal drug exposure was conducted by Streissguth and colleagues. This work examined the effects of alcohol while controlling for the effects of other substances

TABLE 1. Continued

peripherally mediated effects (e.g., on the adrenal medulla and the adrenal cortex).

Chapter IV: Tobacco Use as Drug Dependence

1. Cigarettes and other forms of tobacco are addicting. Patterns of tobacco use are regular and compulsive, and a withdrawal syndrome usually accompanies tobacco abstinence.

2. Nicotine is the drug in tobacco that causes addiction. Specifically, nicotine is psychoactive ("mood altering") and can provide pleasurable effects. Nicotine can serve as a reinforcer to motivate tobacco-seeking and tobacco-using behavior. Tolerance develops to actions of nicotine such that repeated use results in diminished effects and can be accompanied by increased intake. Nicotine also causes physical dependence characterized by a withdrawal syndrome that usually accompanies nicotine abstinence.

3. The physical characteristics of nicotine delivery systems can affect their toxicity and addictiveness. Therefore, new nicotine delivery systems should be evaluated for their toxic and addictive effects.

Chapter V: Tobacco Use Compared to Other Drug Dependencies

1. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

2. Environmental factors including drug-associated stimuli and social pressure are important influences of initiation, patterns of use, quitting, and relapse to use of opioids, alcohol, nicotine, and other addicting drugs.

3. Many persons dependent upon opioids, alcohol, nicotine, or other drugs are able to give up their drug use outside the context of treatment programs; other persons, however, require the assistance of formal cessation programs to achieve lasting drug abstinence.

4. Relapse to drug use often occurs among persons who have achieved abstinence from opioids, alcohol, nicotine,
or other drugs.

5. Behavioral and pharmacologic intervention techniques with demonstrated efficacy are available for the treatment of addiction to opioids, alcohol, nicotine, and other drugs.

Chapter VI: Effects of Nicotine That May Promote Tobacco Dependence

1. After smoking cigarettes or receiving nicotine, smokers perform better on some cognitive tasks (including sustained attention and selective attention) than they do when deprived of cigarettes or nicotine. However, smoking and nicotine do not improve general learning.

TABLE 1. Conclusions of the 1988 Report of the Surgeon General on the Health Consequences of Smoking: Nicotine Addiction (US DHHS 1988).

Major Conclusions

— Cigarettes and other forms of tobacco are addicting.

— Nicotine is the drug in tobacco that causes addiction.

— The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Chapter Conclusions

— In addition to the three overall conclusions of this Report, there are many other substantive conclusions. These points are listed under the appropriate Chapter and Appendix headings.

Chapter II: Nicotine: Pharmacokinetics, Metabolism, and Pharmacodynamics

1. All tobacco products contain substantial amounts of nicotine and other alkaloids. Tobaccos from low-yield and high-yield cigarettes contain similar amounts of nicotine.

2. Nicotine is absorbed readily from tobacco smoke in the lungs and from smokeless tobacco in the mouth or nose. Levels of nicotine in the blood are similar in magnitude in people using different forms of tobacco. With regular use, levels of nicotine accumulate in the body during the day and persist overnight. Thus, daily tobacco users are exposed to the effects of nicotine for 24 hours each day.

3. Nicotine that enters the blood is rapidly distributed to the brain. As a result, effects of nicotine on the central nervous system occur rapidly after a puff of cigarette smoke or after absorption of nicotine from other routes of administration.

4. Acute and chronic tolerance develops to many effects of nicotine. Such tolerance is consistent with reports that initial use of tobacco products, such as in adolescents first beginning to smoke, is usually accompanied by a number of unpleasant symptoms which disappear following chronic tobacco use.

Chapter III: Nicotine: Sites and Mechanisms of Actions

1. Nicotine is a powerful pharmacologic agent that acts in the brain and throughout the body. Actions include electrocortical activation, skeletal muscle relaxation, and cardiovascular and endocrine effects. The many biochemical and electrocortical effects of nicotine may act in concert to reinforce tobacco use.

2. Nicotine acts on specific binding sites or receptors throughout the nervous system. Nicotine readily crosses the blood-brain barrier and accumulates in the brain shortly after it enters the body. Once in the brain, it interacts with specific receptors and alters brain energy metabolism in a pattern consistent with the distribution of specific binding sites for the drug.

3. Nicotine and smoking exert effects on nearly all components of the endocrine and neuroendocrine systems (including catecholamines serotonin, corticosteroids, pituitary hormones). Some of these endocrine effects are mediated by actions of nicotine on brain neurotransmitter systems (e.g., hypothalamic-pituitary axis). In addition, nicotine has direct

TABLE 2. Use of Alcohol, Marijuana, and Cocaine Among "Never" Cigarette Smokers, "Occasional" Cigarette Smokers, and Daily Cigarette Smokers, by Age Group (Percentages)

	Cigarette Use Pattern			
	Age Group Drug Use	Never	Tried, Never Used Daily	Smoked
Alcohol[1]	12-17	2.7	15.9	38.5
	18-25	12.3	31.9	49.6
	26-34	9.8	23.0	41.3
	≥35	5.6	9.2	20.1
Marijuana[2]	12-17	0.2	3.3	22.7
	18-25	3.3	8.3	37.4
	26-34	2.8	12.9	30.3
	≥35	0.6	1.8	3.8
Cocaine[3]	12-17	0.2	0.8	6.4
	18-25	1.3	4.5	14.2
	26-34	1.8	7.2	15.6
	≥35	0.2	0.3	1.9

[1]Drank five or more drinks in a row on at least 1 day in past 30 days.
[2]Used marijuana more than 10 times.
[3]Used cocaine more than 10 times.

Source: Office on Smoking and Health. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* DHHS Publication No. (CDC) 88-8406. Washington, DC. Supt. of Docs., U.S. Govt. Printing Off., 1988

such as caffeine and tobacco. Nevertheless, some tobacco-related findings emerged. Prenatal maternal cigarette smoking was significantly related to poor attention and poor orientation to a testing display board in 4-year-olds (Streissguth et al. 1984) and to lower infant birth weights (Barr et al. 1984). Assessment of neonatal habituation using a Brazelton scale showed that maternal alcohol and tobacco use in midpregnancy was significantly related to poor habituation and increased low arousal in newborn infants (Streissguth 1986; Streissguth et al. 1983; see also Streissguth et al. 1989, 1986).

These studies clearly establish the adverse impact of maternal tobacco use on growth and behavior. Further studies will be needed to establish the extent and reversity of such effects as well as to identify factors that may either reduce or increase them. Similarly, further study will be required to determine if prenatal nicotine exposure results in physical dependence and the occurrence of a neonatal nicotine withdrawal syndrome.

NEUROPHYSIOLOGIC AND NEUROHORMONAL MEDIATION OF THE EFFECTS OF NICOTINE

Nicotine rapidly enters the brain and is distributed to other organs. This leads to a variety of effects on both the brain and the peripheral nervous system (OSH 1988). These peripheral actions of nicotine may be a factor in continued smoking and other use of nicotine (Ginzel 1987). For example, stimulation of the trachea (windpipe) may play a role in smoking's pleasurable effects (Rose and Hickman 1987; Henningfield

1987b). Most of nicotine's physical and psychological effects are mediated primarily through its action in the brain, however, and these effects appear to be critical to the drug's reinforcing effects in animals and humans (Clarke 1987; Wise and Bozarth 1987; OSH 1988).

Distribution and Actions of Nicotine in the Brain

The finding that radioactively labeled nicotine (^{3}H-nicotine) binds to specific brain cells in rat brain (Yoshida and Imura 1979; Martin and Aceto 1981; Marks and Collins 1982), made it possible to visualize (Clarke et al. 1984) and quantify (London et al. 1985b) these brain binding sites by light microscope autoradiography. Nicotine's effects on local cerebral glucose utilization correlate with the distribution of the nicotine binding sites (Clarke et al. 1984; London et al. 1985a). Interestingly, brain areas in which local cerebral glucose utilization is increased by nicotine (see London et al. 1985a, 1986) are similar to the areas that other studies of drug and electrical self-administration suggest are important in reinforcement. These areas of the brain also play a role in other kinds of drug use or behavior that is found to be satisfying or pleasurable (Wise 1980; Nakajima 1984; Wise and Bozarth 1987). Studies by London and others have also shown that the effects of nicotine on local cerebral glucose utilization are directly related to the dose. These effects can be prevented by pretreating the experimental animals with a chemical (mecamylamine) that blocks nicotine's action (London et al. 1988a,b).

Brain Nicotine Receptors and New Nicotinic Agents

Research on specific brain receptors for nicotine—so-called nicotinic receptors—has progressed rapidly (cf. Henningfield and Goldberg 1988). This progress has been due partly to adapting strategies that were first used to identify subpopulations of opioid receptors (cells in the brain that are specific receptors for narcotic drugs). It is now clear that there are multiple types of nicotinic receptors that can be differentiated on the basis of their amino acid sequence (Colquhoun et al. 1987), and binding affinities (see Loring and Zigmond 1987; Loring et al. 1989; Sloan et al. 1988), and that these have different functional properties (see Wonnacott et al. 1987). In addition, new methods are being developed to identify nicotinic receptors. For example, Abood and colleagues (1987) reported using two anti-idiotypic antibodies to identify and purify nicotinic receptors from animal (rat) brains.

The diversity of brain receptors for nicotine has both theoretical and practical implications. For example, as early as 1936, Dorsey suggested that the drug lobeline might be a useful aid to smoking cessation, as it mimics some of nicotine's effects. Since then, lobeline has repeatedly been tried as an adjunct to help smokers quit. However, it has had a rather disappointing record of success (Schwartz 1987; OSH 1988). Lobeline's ineffectiveness is, however, quite consistent with recent findings that indicate that lobeline appears not to bind to nicotinic receptors important in the dependence producing effects of nicotine (Sloan et al. 1984, 1988). These results also support earlier data showing that animals also respond differently to lobeline and nicotine (Rosecranz and Chance 1977).

Another series of studies has examined the actions of various nicotinic agonists (chemicals with nicotine-like effects) and antagonists (chemicals that block nicotine's actions partially or completely). These substances are useful tools for basic research and may also help people quit smoking and avoid relapse. Abood and colleagues (1988) have evaluated a series of chemicals for their receptor binding in rats as well as for their ability to produce or reverse some or all of the effects of nicotine. This line of research has the potential to develop more selective nicotinic agonists and antagonists which may also be useful in the treatment of disorders involving the cholinergic nervous system such as Alzheimer's Disease.

Neurohormonal Effects of Nicotine

Nicotine has both direct and indirect effects on several neuroendocrine systems (Balfour 1982; Clarke 1987; Hall and Cissik 1982; Pomerleau and Pomerleau 1984; OSH 1988; Grunberg et al. 1988a). These effects may mediate or at least play some role in the reinforcing actions of tobacco and other nicotine-containing products. A study by Sopori and others (1989) has extended earlier findings by Pomerleau and colleagues (e.g., Pomerleau and Pomerleau 1984) suggesting that some of the effects of cigarette smoking are the results of smoke-induced increases in beta endorphine levels (naturally occurring chemicals in the brain that have morphine-like effects). Sopori and colleagues found that rats and mice exposed to cigarette smoke had reduced pain sensitivity. These analgesic effects were reversed by naloxone, a drug that blocks the effect of morphine. However, a carefully controlled study by Nemeth-Coslett and Griffiths (1986) found that a wide range of naloxone doses have no effect on human cigarette smoking. This suggests that endorphine involvement may not be a determinant of cigarette smoking rates.

In an interesting study of the interaction between cigarette smoking and variations in women's hormonal state, Steinberg and Cherek (1989) studied cigarette smoking at different times in subjects' menstrual cycles and found that subjects puffed cigarettes more frequently while menstruating. These results are consistent with other findings suggesting there are orderly, though complex, interactions between cigarette smoking and hormonal regulation (OSH 1988).

These studies illustrate the wide diversity in approaches used to explore the interactions between nicotine administration and deprivation and endocrine function. Such strategies hold considerable promise for unraveling these complicated and important appearing factors in the nicotine dependence process.

DEPENDENCE POTENTIAL OF NICOTINE

Although the basic actions of nicotine that so readily produce dependence have been documented in considerable detail (e.g., OSH 1988), continuing research is helping scientists to understand more fully the multiple mechanisms by which nicotine produces dependence, the dependence process itself, and even other forms of drug dependence. One practical application of this research is testing whether nicotine in other dosage forms can help cigarette smokers quit. For example, Craft and Howard (1988) showed that rats were able to recognize nicotine-related stimulation regardless of how the nicotine was given (by mouth, by injection, through the skin, or by other means), although the cue was weaker when they received the drug by means of a skin patch.

Measurement of Tobacco Intake and Nicotine Metabolism

Methods to measure nicotine intake and the drug's biological transformation in the body—its metabolism—have also been improved. Jacob et al. (1988b) reported on the use of radioactively labeled nicotine isotopes to assess nicotine clearance under actual smoking conditions (see also Shulgin et al. 1987). To further refine practical methods of measuring nicotine consumption, Jarvis and others (1988) studied the elimination of cotinine, a metabolite of nicotine, in human samples of plasma, saliva, and urine. They found that cotinine elimination rates required similar amounts of time in each body fluid with average plasma half-lives of approximately 16 hours. Thus, accurate estimates of exposure to tobacco smoke can be based on blood, saliva, or urine samples. Langone et al. (1988) assessed the value of an alternative test for measuring cotinine in saliva and urine (using a so-called monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA) technique). This approach may be more practical and less expensive for accurately measuring tobacco use in large-scale

population studies and after intervention efforts. The Lagone study found that detected levels of nicotine in children were strongly correlated with the number of cigarettes others smoked in the home. In adult smokers there was a positive correlation between salivary and urinary cotinine and a close relationship between levels of urinary cotinine and the number of cigarettes smoked. These data indicated that the ELISA technique may be able to provide a reliable means for measuring both active and passive exposure to tobacco smoke.

Tobacco Self-Administration as a Function of Nicotine Dose

It is now clear that much of the pleasure derived from tobacco products is because of both structural alterations (such as increased nicotine receptors) and functional changes (such as activation of nicotine receptors and the release of neurohormones) in the brain (OSH 1988). Smoking and other means of nicotine ingestion also provide the user with a flexible way of adjusting nicotine intake (Dunn 1972 reported in Henningfield 1988a). Smoking may provide additional stimuli that contribute to the strength of the dependence (e.g., Rose 1988; OSH 1988).

In recent studies in which cigarette smokers were treated with nicotinic antagonists, earlier findings by Stolerman and others (1973) have been extended. Nemeth-Coslett and colleagues (1986) showed orderly dose-dependent increases in several measures of cigarette smoking when volunteers were given mecamylamine. Pomerleau and others (1987) found that people would self-administer high levels of nicotine that would have been unpleasant had they not received a nicotine antagonist (mecamylamine) before smoking. Rose and co-workers (1989) showed that pretreating smokers with mecamylamine not only shifted their preference to higher dose levels of nicotine, but also reduced their subjective ratings of the "harshness" of tobacco smoke.

Benowitz and colleagues (1988) have found that single doses of nicotine gum (nicotine polacrilex) produce both lower peaks and lower overall levels of plasma nicotine and heart rate increases than do cigarettes, oral snuff, or chewing tobacco. Absorption of nicotine from snuff and chewing tobacco accelerated quickly; maximal levels were achieved within about 5 minutes. Nicotine levels obtainable from cigarettes and nicotine gum are limited by the amount of nicotine freely available from the product itself. However, with snuff and chewing tobacco, these amounts can be readily varied by the quantity placed in the mouth. The average intake of nicotine in subjects chewing 7.9 grams of tobacco was 4.5 mg, or about the equivalent from 4 cigarettes or 5 to 6 pieces of nicotine gum (the 2-mg-per-piece type available by prescription in the United States).

Using methods developed to assess smoking outside of the laboratory, Hatsukami and others (1988a) measured the frequency and duration of cigarette puffs in smokers. They found that the frequency of smoking was more closely related to overall nicotine intake and its metabolic half-life than it was to the puffs taken of individual cigarettes. Smokers in whom nicotine levels remained high longer also smoked less frequently (that is, had longer intervals between cigarettes). Another study looked at the use of smokeless tobacco by individuals outside the laboratory (Hatsukami et al. 1988c). This study revealed significant relationships between cotinine levels and the duration and number of "dips" (uses) per day, with the highest frequency of use in the afternoon and evening. These studies demonstrated that patterns of tobacco use are determined both by the dose of the nicotine delivering product as well as by the individual's rate of nicotine metabolism. As reviewed elsewhere in this chapter, additional nicotine and nonnicotine involving factors also contribute to this complex but orderly form of drug abuse.

Changing the number or kinds of cigarettes smoked can also affect smokers' behavior (OSH 1988). Benowitz and others (1986a) studied the effects of smoking fewer cigarettes on exposure to

tar/nicotine and carbon monoxide. They found that the potential health benefits of reducing the number of cigarettes were greatly eroded by an increased intake of tobacco toxins per cigarette because habitual smokers compensate for the decrease in cigarettes by inhaling more smoke per cigarette. The intake of tobacco toxins increased roughly threefold per cigarette; for example, daily exposure to carbon monoxide declined only 50 percent despite a reduction of over 86 percent (from 37 to 5 cigarettes) in the average number of cigarettes smoked per day.

Cinciripini and colleagues (1989) measured the variability of plasma nicotine levels when subjects smoked cigarettes of different nicotine contents. They found that heavy smokers made more precise adjustments in their nicotine intake when smoking lower nicotine cigarettes than did light smokers. Light smokers also responded with less variability to cigarettes with higher nicotine levels (they did not alter their smoking behavior as much despite the higher levels of nicotine they were getting from the "stronger" cigarettes).

Tolerance

Nicotine tolerance has been studied since shortly after the turn of the century (Henningfield and Goldberg 1988, OSH 1988). The rapid development of tolerance to nicotine is so pronounced that it plays a major role in the relatively rare occurrence of deaths due directly to nicotine poisoning. One illustration of this was reported by Benowitz and colleagues (1987): A cigarette smoker soaked her skin with an insecticide containing 40 percent nicotine sulphate. Although her blood levels of nicotine were very high (more than 300 ng/ml), the patient developed tolerance to the intoxication, nausea, vomiting, and abdominal cramps from her nicotine poisoning and she survived. Several investigators have studied the time relationships involved in developing and losing nicotine tolerance. For example, Aceto and others (1986) measured blood pressure and heart rate in rats that had been given nicotine. When the doses were given at 30-minute intervals, tolerance was not observed, but at 1-minute intervals, tolerance developed quickly after 4 to 6 injections, depending on the dose. This suggests that nicotine tolerance is related to both frequency of nicotine administration and dose. Porchet and coworkers (1987) studied the development of tolerance to intravenous nicotine administration in rabbits and humans using measures of heart rate change and blood plasma nicotine concentration. Their study showed that the diminished response to single doses of nicotine (often termed "acute tolerance" or "tachyphylaxis") is at least partly due to the distribution kinetics of nicotine (see also Porchet et al. 1988).

Physical Dependence

Despite important advances in knowledge in recent years, physical dependence on nicotine and treatment of the nicotine withdrawal syndrome are still important research issues. For example, it is now clear that severity of nicotine dependence can be at least approximately determined using behavioral and biochemical diagnostic approaches, and that severity is a factor in quitting difficulty, withdrawal symptom severity, and likelihood of relapse after quitting (OSH 1988). Further refinements in diagnostic techniques and identification of the most effective treatments as a function of dependence level will undoubtedly be important to advances in treatment. The essential features of the syndrome and its associated features, course, and differential diagnosis are described in table 3.

Recent studies have confirmed earlier observations that the magnitude of tobacco withdrawal symptoms is directly related to the amounts smoked or otherwise consumed (Killen et al. 1988; see also Henningfield 1988b; OSH 1988). The relationship has not always been observed, however, when only crude indices of the level of nicotine use and/or assessment of withdrawal symptoms were used (OSH 1988). An interesting new finding is that the assessment of withdrawal symptoms may be complicated by an acute increase in plasma caffeine levels occurring after a

TABLE 3. Description of the Nicotine Withdrawal Syndrome in the Diagnostic and Statistical Manual of the American Psychiatric Association, III-Revised (American Psychiatric Association 1987)

Nicotine Withdrawal

The essential feature of this disorder is a characteristic withdrawal syndrome due to the abrupt cessation of or reduction in the use of nicotine-containing substances (e.g., cigarettes, cigars, and pipes, chewing tobacco, or nicotine gum) that has been at least moderate in duration and amount. The syndrome includes craving for nicotine; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain.

In many heavy cigarette smokers, changes in mood and performance that are related to withdrawal can be detected within 2 hours after the last tobacco use. The sense of craving appears to reach a peak within the first 24 hours after cessation of tobacco use, and gradually declines thereafter over a few days to several weeks. In any given case it is difficult to distinguish a withdrawal effect from the emergence of psychological traits that were suppressed, controlled, or altered by the effects of nicotine or from a behavioral reaction (e.g., frustration) to the loss of a reinforcer.

Mild symptoms of withdrawal may occur after switching to low tar/nicotine cigarettes and after stopping the use of smokeless (chewing) tobacco or nicotine gum.

Associated features. Increased slow rhythms on an EEG, decreased catecholamines, decreased metabolic rate, tremor, increased coughing, REM change, gastrointestinal disturbance, headaches, insomnia, and impairment of performance on tasks requiring vigilance are commonly associated features of nicotine withdrawal.

Course. The symptoms begin within 24 hours of cessation of or reduction in nicotine use and usually decrease in intensity over a period of a few days to several weeks. Some former nicotine users report that craving for the substance continues for longer periods.

Differential diagnosis. The diagnosis of nicotine withdrawal is usually self-evident from the person's history, and disappearance of the symptoms if smoking is resumed is confirmatory. However, withdrawal from other psychoactive substances may take place simultaneously, and produce similar symptoms.

Source: American Psychiatric Association 1987

person quits smoking. Even though caffeine ingestion (through coffee, tea, soft drinks, etc.) remains the same, Brown and others (1988) found that, in cigarette smokers, caffeine levels were 46 percent greater after several days of tobacco abstinence than during smoking; caffeine half-lives were longer when not smoking (3.37 hours versus 3.09 hours during smoking). The possible clinical implications of this nicotine-caffeine interaction are illustrated in a case study by Sachs and Benowitz (1989), who found that symptoms of an apparent nicotine withdrawal syndrome (insomnia, increased weight, increased anxiety, and possibly restlessness) may have been partially the result of acute increases in plasma caffeine levels resulting from the diminished rate of caffeine metabolism.

One series of studies systematically evaluated the tobacco withdrawal syndrome outside the laboratory (Hughes and Hatsukami 1986; Hatsukami et al. 1988a; Hatsukami et al., manuscript submitted). These studies confirmed that a withdrawal syndrome occurs reliably in chronic smokers, that the qualitative symptom profile is similar to but of greater magnitude than that seen in the laboratory, and that most signs and symptoms of withdrawal can be prevented by ingesting nicotine in the form of nicotine gum. Withdrawal symptoms that accompanied abstinence from smokeless tobacco were generally similar to those following cigarette abstinence (Hatsukami et al. 1987).

When smokers are acutely deprived of tobacco, various measures of performance as well as the electrophysiologic correlates of performance are adversely affected (OSH 1989; see also table 1). One series of studies measured changes in behavior, physiology, and performance caused by nicotine abstinence over time and after smoking was resumed (Snyder and Henningfield 1989; Snyder et al. 1989; Pickworth et al., in press). Similar testing showed that most of the effects of discontinuing tobacco use could be reversed by providing nicotine in chewing gum form in amounts proportional to the earlier nicotine dose level obtained from smoking (Snyder and Henningfield 1989; Pickworth et al., in press). Another study compared the effects of short-term cigarette deprivation for smokers and smokeless tobacco deprivation for smokeless tobacco users (Keenan et al. 1989). Increased reaction times on performance measures corresponded to the increase in self-reported withdrawal symptoms and to the decrease in heart rate. Using a sustained attention task, Hughes and colleagues (1989) evaluated the performance of nonsmokers and of abstaining and smoking cigarette smokers. They found that abstinence increased response variability and appeared to impair the ability to inhibit response, although it did not increase fatigue (Pickworth et al., in press).

It is known that young people can become readily addicted to tobacco products (National Institutes of Health (NIH) 1986b), and a recent study has shown that such use can also result in early physical dependence on nicotine. Ershler and others (1989) interviewed 622 6th through 12th graders who had attempted to quit smoking, and then reinterviewed them 2 years later. More than 80 percent of those who smoked reported trying to quit. Eighty percent of the quitters were again smoking at the time of the first interview. At the time of the 2-year followup interview, 71 percent were still smoking. As with adults, the severity of withdrawal symptoms and difficulty in quitting were related to prior smoking levels.

INDIVIDUAL FACTORS IN THE ETIOLOGY OF TOBACCO USE AND NICOTINE'S EFFECTS

Not all people are equally likely to begin smoking, and there is wide variation in the difficulties people have when they try to quit (OSH 1988, 1989). These everyday observations are consistent with the fact that rates of cigarette smoking can vary widely over relatively short periods of time, as a function of such factors as the availability and price of cigarettes and the social acceptability and perceived risk of smoking (cf. OSH 1988, 1989). In addition, there appear to be individual differences in susceptibility or vulnerability to becoming dependent on tobacco that are important to prevention and intervention efforts. For example, differences in personality and development suggest that different prevention approaches may be required at different ages (Leventhal et al. 1988).

The broad range of factors associated with an increased risk of becoming dependent on tobacco are similar to those associated with dependence on other addictive drugs. These include stressful environments (OSH 1988), genetic predisposition (Hughes 1986), and behavioral disorders in youth (Brown and Mills 1987; Welte and Barnes 1987; Kumpfer 1987). Personality traits such as shyness and aggressiveness, observed in children as young as 6, have been found to correlate with adolescent tobacco and drug use (Kellam et al. 1980, 1982). Tobacco use may also affect vulnerability to the use of other illicit drugs. Even though caffeine and alcohol are often associated with nicotine as "gateway drugs" to illicit drug use (Kandel 1975; OSH 1988), the role of nicotine may be still more pronounced when it is the first drug on which the user becomes dependent (Ershler et al. 1989; OSH 1988; Henningfield et al., in press; see also table 2).

One series of studies examined the relationship between early childhood experiences and smoking and also studied factors that may have moderating effects. Brook et al. (1987) studied the relationship between fathers' and daughters' smoking and the personality

characteristics, such as inherent protective factors, that were involved in the daughters' decision to begin smoking. This research and a study of 638 mother-daughter relationships (Brook et al. 1989) identified risk factors related to early experience and to the parent-daughter relationship. Both studies also identified factors that reduced the impact of early risk factors on later adolescent drug involvement.

A study of smoking and peer group affiliation also revealed specific factors associated with cigarette smoking. Mosbach and Leventhal (1988) studied this relationship in junior high school students. They found that over half (56 percent) of the smokers were from two high-risk groups that constituted only 15 percent of the total sample. These findings suggest that smoking and drug prevention programs could be more specifically directed toward identifiable subgroups.

A number of animal studies have focused on genetic determinants of nicotine dependence. Researchers who studied differences in response to nicotine, and in central nicotinic receptors among strains of rats and mice, found that mouse strains that are more sensitive to nicotine-induced seizures also had greater numbers of hippocampal nicotine receptors (Miner et al. 1984, 1986). This work has been extended to other mouse strains to examine the effect of genetic factors on sensitivity or innate tolerance to nicotine, behavioral and physiologic response to nicotine, and how these relate to the brain nicotinic receptors (Collins et al. 1988).

Weight and Appetite

Cigarette smokers weigh less than nonsmokers of the same age, and many smokers who quit smoking gain weight (OSH 1988; see also table 1). This relationship may play an important role in initiation and cessation of smoking and in affecting smoking relapse (OSH 1988). The apparent interaction between susceptibility to weight gain, effectiveness in controlling weight gain, and the possible use of eating to reduce withdrawal is an important ongoing area of research. For example, Hall et al. (1986) found that people tended to gain weight within the first 26 weeks after cessation of smoking. The amount of weight gain was directly related to the number of cigarettes previously smoked. Persons who had smoked 30 or more cigarettes per day gained approximately 11 pounds; those who had smoked fewer than 10 cigarettes per day gained only about 3 pounds. However, smoking relapse was not predicted by weight gain. Although weight gain may play a role in some cases of relapse (OSH 1988), these data suggest that, for some people, it may help to reduce tobacco withdrawal symptoms, nicotine-seeking behavior, or both. This has been shown with other dependence-producing drugs in several other animal species (Carroll and Meisch 1984; Griffiths et al. 1980).

Interactions between appetite, eating, mood and smoking also appear important in the nicotine dependency process. Duffy and Hall (1988) assessed eating and mood changes that resulted from 24-hour cigarette abstinence. The results of this study may help to determine subpopulations of cigarette smokers who would like to quit but who may be more predisposed to increased food intake.

Perkins and colleagues have studied the relationship between nicotine, metabolic rate, and physical activity levels in humans. In one study, they showed that nicotine, delivered in the form of a nasal spray, produced acute increases in the resting metabolic rates of human cigarette smokers (Perkins et al., in press, a). These effects were further enhanced during light physical activity, similar to office work (Perkins 1989; Perkins et al., in press, b).

Research with animals has been fundamental in determining the various biological underpinnings of the interactions between nicotine and body weight. For example, rat experiments by Grunberg et al. (1989) found that nicotine inhibits weight gain during early development and that part of the effect may be due to changes in specific appetites (that is, a reduction in carbohydrate preferences). Female rats may be more

susceptible to such changes (Grunberg et al. 1986, 1988, 1987).

The role of water regulation in nicotine's effects on weight was explored by Thomas and co-workers (1988), who found that rats continuously exposed to changes in nicotine for 6 days showed significant dose-related suppression of water intake and body weight decreases for the initial 4 days. Water intake then returned to control levels. These data suggest that water regulation itself may play a significant role in body weight changes that have been found in smokers (see also Grunberg 1982; Levin et al. 1987).

Studies of the effects of nicotine chewing gum consistently show that nicotine itself plays a role in the body weights of smokers: the more gum used per day, the less weight gained (see also Stitzer and Gross 1988; Fagerstrom 1987). These studies also indicate that the use of nicotine gum can reduce weight gain in ex-smokers. For example, Emont and Cummings (1987) showed that more frequent smokers (26 cigarettes/day) who had higher nicotine tolerance scores gained more weight than those who were less nicotine dependent.

Mood and Affect

Initiation of cigarette smoking is more common when people are exposed to stressful environments, and their smoking rates increase in response to stressful stimuli. Nicotine has been shown to reduce anxiety in both animal and human research (OSH 1988; Pomerleau and Pomerleau 1984; Gilbert and Welser 1988), and smokers report that they obtain calming effects from smoking. Cinciripini and others (1989) studied changes in levels of catecholamine (neurotransmitter chemicals that play a role in mood and affect the reactions to stress and boredom) in smokers and nonsmokers during a computer-controlled reaction time test given at progressively higher levels of difficulty. The study showed that smokers were more responsive than nonsmokers to the catecholamine changes that occurred.

Animal models continue to provide fundamental information about nicotine dependence. Aceto and others (1986) studied the pain-reducing actions of nicotine in rats. They found that this action of nicotine occurred at the level of the spinal cord rather than in the brain. Such research is essential to developing more effective intervention for people who suffer disturbances of mood and affect upon quitting smoking.

DEVELOPMENT OF MORE EFFECTIVE INTERVENTION STRATEGIES

Treatment approaches can be categorized as those that involve medications (pharmacologic treatment) and those that do not (behavioral treatment). Newer pharmacologic and behavioral approaches show considerable promise for treating tobacco dependence, as they have for other drug dependencies (Grabowski and Hall 1985; Ockene 1986; Pomerleau et al. 1988). In discussing recent progress, it is useful to begin with a brief description of two clinical aspects of tobacco dependence. The first is the compulsive use of tobacco itself, despite an awareness of its potential harm and, often, despite repeated efforts to quit. Such use has been classified as a psychoactive substance use disorder (American Psychiatric Association 1987). The second aspect is the physical dependence on nicotine that commonly occurs. In physically dependent persons quitting is accompanied by a nicotine withdrawal syndrome which is classified as an organic mental disorder (see table 3). Research indicates that pharmacologic intervention can be effective in reducing withdrawal symptoms and the likelihood of relapse but that it is more effective when used in conjunction with behavioral intervention such as social support and skills training (Fagerstrom 1988; Hall et al. 1986). Behavioral intervention may also increase patients' adherence to pharmacologic treatment procedures (Epstein and Cluss 1982).

Four pharmacologically based approaches have been differentiated and studied: replacement or sub-

stitution therapy, blockade or antagonist therapy, nonspecific symptomatic pharmacotherapy, and deterrent therapy (Jarvik and Henningfield 1988; OSH 1988). When considering these approaches, it is important to note that, despite the powerful effects of both drug use and discontinuance, most drug-dependent persons (possibly excluding opioid users) do not require systematic pharmacologic treatment. Drug-dependent persons sometimes achieve lasting abstinence in the absence of formal treatment programs or even years after receiving treatment (see discussion of "spontaneous remission" in OSH 1988). On the other hand, it is growing evident that many individuals have great difficulty quitting smoking and may require medical support.

Pharmacologic Treatment of Nicotine Dependence

The temporary use of nicotine preparations to replace the nicotine obtained from tobacco is a well-established pharmacologic intervention for nicotine dependence (OSH 1988). Nicotine polacrilex (chewing gum) has been studied and is the only medication approved by the FDA for the treatment of nicotine dependence. Important recent research advancements in the use of nicotine gum have included increased understanding of the required doses and of their effects (Henningfield and Woodson 1989).

Benowitz and colleagues (1988) found that smokers ingested 36 mg of nicotine per day when smoking their own cigarettes, 15 mg of nicotine when using 4 mg/dose nicotine gum, and 10 mg when using 2 mg/dose gum. Subjects actually appeared to absorb about .86 mg of nicotine per 2 mg dose (the commercially available dose). Studies at the Addiction Research Center in Baltimore (e.g., Pickworth et al. 1986, 1988) also found that people obtained lower nicotine dose levels than were anticipated from the use of nicotine gum. Specific determinants of the amount of nicotine obtained were the rate of chewing (Nemeth-Coslett et al., 1988) and the level of consumption of such acidic beverages as coffee or soft drinks, which reduce nicotine absorption (Henningfield et al., in press). Controlling these factors makes it possible to control doses more accurately in experimental studies (e.g., Nemeth-Coslett et al. 1987), and should also increase the clinical efficacy of this treatment (cf. Jarvik and Henningfield 1988b; Sachs 1989).

Identifying patient populations that are most likely to benefit from nicotine replacement therapy has been a major challenge. For example, there is a direct, though crude, relationship between nicotine intake and the magnitude of withdrawal symptoms and difficulty in quitting smoking (OSH 1988; Russell, in press). One study found that simply categorizing subjects as smokers of fewer than 16 or of more than 24 cigarettes per day was predictive of the severity of their nicotine dependence (Killen et al. 1988). For more selective diagnoses, other objective criteria such as the Fagerstrom tolerance questionnaire, and biological measures of nicotine or smoke exposure, may also be useful (Henningfield 1988; OSH 1988).

Improvement of diagnoses is important, as the 2 mg/dose nicotine gum now available in the United States appears to be most useful with moderately dependent smokers. Light smokers' tobacco use appears to be more heavily controlled by factors other than nicotine intake. Heavy smokers, by contrast, may not be able to extract sufficient amounts of nicotine from the nicotine gum (see Hall et al. 1987; Tonneson et al. 1988).

Research findings (OSH 1988; Jarvik and Henningfield 1988; Hughes et al., in press) suggest that nicotine gum is most useful in helping people to achieve abstinence, reducing withdrawal signs and symptoms, preventing relapse while patients are maintained on the gum, and, possibly, encouraging patients to stay in treatment programs. Nicotine in this form is not reliable in reducing the urge to smoke (which is elicited by many nonpharmacologic subjective and environmental stimuli), and does not necessarily reduce rates of relapse subsequent to termination of its use. One practical implication of these facts is that the length of time this medication is used should be deter-

mined in the individual case, based on specific need to avoid relapse to tobacco use (see Jarvik and Henningfield 1988).

Other Pharmacologic Approaches

Antagonist therapy: As described earlier, studies involving a nicotine antagonist (mecamylamine) have extended the initial findings of Stolerman et al. (1973), although this antagonist has not yet been systematically evaluated for clinical efficacy (cf. Stolerman 1986; Jarvik and Henningfield 1988). Symptomatic therapy: The drug clonidine has been the subject of some preliminary evaluation for symptomatic treatment. Clonidine was found to reduce craving scores in a tobacco abstinence study (Glassman et al. 1984). However, its usefulness as an aid to smoking cessation remains to be fully explored; preliminary data are mixed. In one study, clonidine use for approximately 6 weeks resulted in significantly higher rates of abstinence at the 6-month followup evaluation in female but not in male smokers (Glassman et al. 1988). Another study found that clonidine had no significant effect in helping people to quit smoking beyond the first week of abstinence (Davison et al. 1988). Other symptomatic treatment approaches have been discussed (Jarvik and Henningfield 1988; OSH 1988), but have also not been systematically studied (Schwartz 1987). These include the use of minor tranquilizers (benzodiazepines) to treat ex-smokers who suffer from chronic anxiety and the use of antidepressant drugs for those who become clinically depressed when they quit (see Glassman et al. 1988). Deterrent therapy: Deterrent approaches, in principle, could be of enormous potential utility; however, a satisfactory deterrent has yet to be developed (Jarvik and Henningfield 1988). Most recently, a gum preparation of silver acetate has been tested as a means to maintain abstinence for tobacco smoke (Malcolm et al. 1986). What appears to be needed is longer acting deterrents and systematic behavioral programs to ensure compliance with therapeutic protocols (Jarvik and Henningfield 1988; OSH 1988).

The variety of methods used to facilitate cessation and prevent relapse (see Henningfield 1987b) is illustrated by a novel treatment approach using citric acid aerosol spray to reduce the urge to smoke (Rose and Hickman 1987). Although not yet evaluated in clinical efficacy trials, this study found that the urge to smoke could be reduced by such peripheral stimulation.

Gradual Nicotine Withdrawal

Attempts to enable cigarette smokers gradually to reduce their nicotine intake by decreasing the number of cigarettes smoked or by smoking cigarettes that deliver less nicotine have often been defeated by such compensatory changes in smoking behavior as inhaling more deeply or smoking a larger number of the low-nicotine cigarettes (McMorrow and Foxx 1983; Kozlowski 1986; OSH 1988; Benowitz et al. 1986a,b). A new approach to reducing nicotine intake using a pocket-size computer to assist smokers in gradually reducing their cigarette consumption has been described by Prue and colleagues (1989). Use of this program produced quarterly reductions in tobacco intake that were verified by objective cotinine and carbon monoxide measures as well as by the number of cigarettes smoked. Hatsukami and colleagues (1988a) examined the occurrence of acute withdrawal symptoms under everyday smoking conditions using three methods of smoking cessation. They found that after 3 days of unrestrained smoking there were no significant differences in the severity of withdrawal symptoms between partial reduction groups (that is, a group that reduced its cigarette consumption by half compared to a group in which nicotine yield per cigarette was correspondingly reduced), but that the withdrawal symptoms were significantly lower in the partial reduction subjects than in subjects who stopped completely.

Relapse Prevention Approaches

Following cigarette smoking cessation, rates of relapse are highest during the first days and weeks and diminish considerably after three months abstinence (OSH 1988; Kottke et al. 1989). Relapse prevention approaches have recently been extensively reviewed (Schwartz 1987; OSH 1988), revealing advances in both understanding and intervention approach. For example, one study (Havassy et al. 1987) evaluated social support measures to prevent relapse to tobacco, alcohol, and opiate use. Their initial findings confirm that systematic social support measures help maintain abstinence by former users of all three drugs. This study also found that a significant other, such as a spouse, was particularly critical in preventing early relapse.

Minimal Intervention and Workplace Programs

It has often been recommended that physicians adopt at least minimal intervention strategies to encourage and assist their patients in quitting smoking (Hughes and Kottke 1986; Sachs 1989; Russell et al. 1979). Several studies have confirmed that such efforts can be substantially enhanced by prescribing nicotine gum (Russell et al. 1983; Fortmann et al. 1988; Jamrozik 1984; Hughes et al. 1989). The Hughes et al. (1989) study suggested that although quitting efforts were enhanced by nicotine delivering gum in a minimal intervention approach, overly strong pressure by clinicians to rapidly terminate use of the medication by patients may lead to relapse and thereby reduce the potential benefit of the therapy. Recent publications provide useful instructions to physicians who wish to help their patients quit (e.g., American Lung Association 1988; Schneider 1988; Cooper and Clayton 1988; Sachs 1989; Jarvik and Henningfield 1988). These approaches are a potentially cost-effective means of helping those smokers who would like to quit (4 of 5 smokers, or about 40 million people) (Harris et al. 1987; OSH 1988). Another cost-effective approach is intervention in the workplace. Initial findings of research on such programs support their efficacy but also indicate the importance of more effective methods to maintain—not simply achieve—abstinence (Jason et al. 1987a,b; Jason et al., in press).

Treatment of Those with Tobacco-Caused Disease

Although tobacco-caused diseases are a significant factor that may lead to abstinence (OSH 1988), persons with such diseases are often among those who have the greatest difficulty in remaining abstinent (Burling et al. 1984; West and Evans 1986; Perkins 1988). NIDA-supported researchers have recently begun developing treatment programs directed specifically toward these patients. For example, a study of chronically ill cigarette smokers (Carmody et al. 1988) provided practical clinical information for treating such groups. It was found that a successful treatment outcome was related to pretreatment reductions in cigarette smoking levels as well as to the prescription of nicotine gum. Another report described a promising behavioral approach for assessing and treating tobacco dependence in patients with chronic obstructive pulmonary disease (Crowley et al. 1989).

Alternate Nicotine Delivery Systems

The rationale for developing alternative systems of nicotine delivery for medicinal use is based upon the highly toxic nature of tobacco-based systems and the concomitant diversity of patient needs and preferences. These observations have found objective therapeutic benefits from nicotine administration to those trying to quit smoking. A broader range of dosing options may also enhance efforts to reduce smoking prevalence with less risk of dependence or other adverse effects that result from the delivery system itself (Russell 1988; OSH 1988). One promising approach is the nicotine transdermal patch, a skin patch that delivers a relatively constant amount of nicotine. A research team initially found that such a patch could effectively deliver nicotine doses (Rose et al. 1984); they subsequently found that it could also

reduce cigarette craving and nicotine self-administration in preference tests (Rose et al. 1986). Two multicenter clinical trials of the transdermal patch have now been initiated by pharmaceutical firms in the United States. In addition, researchers at the Addiction Research Center in Baltimore have begun studies of the safety, mechanism of action, and abuse liability of this approach.

Other potentially useful alternative nicotine delivery systems have also been studied. For example, a nasal droplet solution of nicotine has been described (Russell et al. 1983; West et al. 1984; Jarvis 1986; Russell et al. 1988). This system seems to reduce withdrawal symptoms and has been found effective in one preliminary trial (Jarvis 1986). Another nasal spray system (Perkins et al. 1986) has also been used experimentally to give controlled doses of nicotine to human volunteers (Perkins et al. 1989; in press, a). The nicotine vapor inhaler technology originally described by Jacobson and colleagues (1979) has also been studied in greater detail in recent years. Preliminary research suggests that such an approach may be useful in reducing the urge to smoke, even though use may not produce reliable systemic nicotine absorption (Sepkovic et al. 1986; Russell et al. 1987; Henningfield 1986).

Evaluation of Alternate Nicotine Delivery Systems

Because nicotine delivery systems vary with respect to their toxicity and addictiveness, former Surgeon General C. Everett Koop recommended that all new systems be carefully evaluated (OSH 1988; see also table 1) and regulated as appropriate. For example, the nicotine vapor inhaler described above, a cinnamon or peppermint-flavored chewing gum containing small amounts of tobacco (*Tobacco International* 1987), and a tobacco-containing "toothpaste" all were marketed as "tobacco products" (OSH 1988). However, the Food and Drug Administration (FDA) took action with respect to all three. They removed the vapor inhaler from the market, declaring it to be an unevaluated "new drug." The chewing gum was classified as an "adulterated [with tobacco] food product" and removed from the market. The toothpaste remains on the market, still under review by the FDA, but with its original claim to promote dental hygiene removed (Committee On Energy and Commerce 1989). Another system, a carbon- ("charcoal-") burning nicotine vapor inhaler patented as a drug delivery device (Committee On Energy and Commerce 1986; *Charlotte Observer* 1987; *Washington Post* 1987) was marketed for approximately 5 months as a cigarette. Although marketing terminated before the FDA issued an opinion regarding its regulatory status, the FDA had been advised by several health organizations and Federal institutes (including NIDA, see Committee On Energy and Commerce 1989) that this device should be regulated in accordance with its patent claims, that is, as a "drug delivery system" and/or a "new drug." An additional concern of NIDA was the device's potential use with illicit substances such as smokable cocaine: the device could facilitate the surreptitious use of such drugs (Committee On Energy and Commerce 1989). The patent itself indicates that the inhaler could be used or modified for use with various other drugs (Committee On Energy and Commerce 1988). A research monograph documented the device's effectiveness at nicotine delivery (R.J. Reynolds 1988), and machine tests confirmed that the inhaler can easily be modified to yield cocaine vapor (Cone and Henningfield 1989).

DEVELOPMENT OF MORE EFFECTIVE PREVENTION STRATEGIES

Reducing tobacco use among youth is important not only in its own right, but perhaps as an important step in reducing other kinds of drug dependence as well (NIH 1986; OSH 1988; Henningfield, Clayton, and Pollin, in press). Efforts to prevent tobacco dependence have had practical public health value. For instance, studies have shown that prevention efforts can be undertaken in grade school programs using peer student leaders and teachers (Murray et al. 1984) and

by teaching coping skills to enable students to resist pressures to experiment with tobacco and other drugs (Flay et al. 1983). A major multicommunity trial funded by NIDA demonstrated that significant reductions in the prevalence of use of tobacco, alcohol, and marijuana in adolescents, could be achieved by use of a broad spectrum drug abuse prevention program (Pentz et al. 1989). Such studies demonstrate both the promise and importance of prevention programs that target tobacco along with other addictive psychoactive substances in reducing drug abuse in general.

Other prevention research is providing new insights that may increase the efficacy and efficiency of prevention programs for tobacco and other substances. For example, to facilitate early prevention efforts, Leventhal and colleagues have collected data on the beliefs and attitudes of students and the psychosocial processes related to their drug use or nonuse. In one study (Leventhal et al. 1987), they examined beliefs about smoking and risk factors based on interviews with 895 urban, public school children in grades 2 through 12. They found that the youthful respondents greatly overestimated the prevalence of adult and peer smoking. Negative attitudes of their peers toward smoking were greatly underestimated. A large proportion believed that they would be less likely than other people to contract smoking-related illnesses and had poor understanding of the tobacco-dependence process.

Cost has been demonstrated by basic researchers to function as a potent source of control of drug intake and possibly of initiation of drug use (Griffiths et al. 1980; Henningfield, Lukas, and Bigelow 1986). Tobacco use is similarly affected by manipulations of cost (Stitzer and Bigelow 1983), leading to predictions that prevention efforts could be substantially augmented by increases in the cost of cigarettes (Warner 1986; OSH 1989).

One other component of drug prevention efforts is to reduce access. This is difficult to do with tobacco because it is a legal substance for adult use and widely available. Laws concerning the sale of tobacco to minors are rarely enforced, and free sample distribution programs are widespread (OSH 1989). For example, Davis and Jason (1988) note that from 1975 to 1984, cigarette companies' expenditures for distributing free samples increased from 22.2 million to 148 million dollars per year. They also found that many students from elementary and high schools, as well as from colleges in the Chicago area, had received free samples of tobacco. Such ready access is in sharp contrast to efforts to discourage smoking and other tobacco use by children and adolescents (Altman et al. 1989).

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BASIC RESEARCH ON OPIOID PEPTIDES AND RECEPTORS

INTRODUCTION AND OVERVIEW

Opiate drugs such as heroin and morphine are thought to act by mimicking or amplifying the actions of the naturally occurring substances they resemble. These natural substances are called endogenous opioids or endorphins. Endogenous opioid peptides and their receptors represent one of many systems of communication within the body. The peptides, or short proteins, are synthesized within a cell, are secreted within the brain or in the general circulation, and interact with a larger protein molecule—a receptor—embedded in the outer membrane of another cell.

This receptor constitutes a target that can be either very close to another receptor (as in the case of two adjacent cells in the brain) or quite distant (for example, in another part of the body). Once the peptide has bound to its receptor, the peptide's mission is essentially complete, and the task of the receptor begins.

The peptide is degraded and the receptor now interacts with other molecules near the inner membrane of the cell, starting a new cascade of events, which constitute the second message (the peptide being the first). This second message alters the activity of the cell in a variety of ways, from changing gene transcription to altering electrical conditions and leading to further repercussions. Endogenous opioids and their receptors are part of a well-orchestrated network of activity in the body, involved in such physiological functions as sensitivity to pain, responsiveness to stress, reward mechanisms, endocrine control, motor coordination, and learning and memory.

To understand opioid functions and the ways that drugs of abuse affect them, one must understand the peptides as the first messengers, and the receptors and the ways in which they couple to their second messengers. In addition, one must understand the framework in which these two classes of elements operate, that is, how and when peptides and receptors are made, where they are expressed in the body, and how they react to various bodily needs and control various bodily functions. Finally, one needs to understand the dynamics of the first and second messenger systems for the endogenous opioids in addiction, chronic pain, and depression.

Understanding these processes is a major undertaking, especially as endogenous opioid systems do not exist in isolation but are constantly interacting with other equally dynamic systems. However, a great deal of the basic information has been gathered in the past 15 years, providing the cornerstone of knowledge needed to explore the more complex aspects of opioid systems. Understanding of the peptides has moved very rapidly, from ignorance of their existence to full knowledge of their chemical sequence, gene structure, distribution in the brain and outside it, and the control of their synthesis and metabolism. Knowledge of opioid receptors is less complete. Although it is known that numerous receptors exist, and there are highly selective drugs with which to label them, their protein or gene structures, and even their exact numbers, are still unknown. Nevertheless, a great deal of work has helped define the distribution of those receptors that can be identified, their coupling to second messengers, and their involvement in various functions and behaviors. Finally, the area that requires the greatest effort is understanding peptide-receptor interactions in a physiological context and defining the role of opioids and their many receptors in functions such as reward mechanisms, pain, stress, and affect. Founded on a basic knowledge of biochemical and cellular structure, this knowledge of opioids and how they affect behavior will eventually lead to a scientific framework for understanding the biology of opiate abuse.

THE ENDOGENOUS OPIOID PEPTIDES

It is now certain that all endogenous opioid peptides belong to a single family of genes comprising three distinct genes, termed Pro-Opiomelanocortin (POMC), Proenkephalin (Pro-Enk), and Prodynorphin (Pro-Dyn). Each of these genes contains one or more active opiate peptides, as well as other nonopioid peptides; beta-endorphin, which derives from pro-opiomelanocortin, is the longest peptide that interacts with opioid receptors. It is extremely active in the test tube, in animals, and in humans. It can produce profound pain relief (analgesia) and, upon repeated administration, can lead to tolerance and physical dependence. It has been implicated in phenomena such as stimulation-produced analgesia (Millan et al. 1987). The proenkephalin precursor gives rise to seven peptides, all enkephalins, containing the opioid core tyr-gly-gly-phe-leu (leu-enkephalin) or tyr-gly-gly-phe-met (met-enkephalin) with various extensions. They are shorter acting than beta-endorphin and behave as classical neurotransmitters (Eiden 1987). Finally, prodynorphin gives rise to three opioid peptides that contain the leu-enkephalin sequence at their amino termini, called dynorphin A, dynorphin B, and neo-endorphin. These peptides have a wide range of duration of action and a complex pharmacological profile, as will be discussed below.

The general distribution of these peptides in the central nervous system was fairly clear at the time of the Second Triennial Report (see Khachaturian et al. 1985), although new findings have emerged through the use of molecular biology for localization in non-neural cells (see below). The general steps involved in the synthesis of these peptides were known to proceed from transcription of a specific gene making a messenger RNA (mRNA), to translation of this mRNA into a protein precursor (e.g., POMC, Pro-Enk, or Pro-Dyn) to further cutting of this precursor into smaller biologically relevant peptides, a step called post-translational processing. These steps were fairly well defined for POMC in the pituitary gland (where it is expressed in abundance) and less well understood in the brain (Smith and Funder 1988). Even now they remain very sketchy for prodynorphin and proenkephalin (Costa et al. 1987).

In the past 3 years, the use of molecular biological techniques has had the single biggest impact in expanding our knowledge of the opioid peptide systems, from expression of the genes for the precursors to formation of the final products and the regulation of these processes by physiological events.

Cloning of Opioid-Related Enzymes

The cloning of the enzymes involved in the biosynthesis and metabolism of the opioid peptides has lagged behind the characterization of the peptides themselves. In the past 3 years, efforts in this direction have begun. For example, an enzyme called PAM (peptidylglycine alpha-amidating monooxygenase), which is critical for amidation, the last step of post-translational processing of many peptides, has recently been purified and cloned by Eipper and her coworkers (Murthy et al. 1986, 1987). Another enzyme thought to be responsible for degrading enkephalin and other peptides, called enkephalinase, has also been cloned from rat and human libraries (Malfroy et al. 1987, 1988). A number of other investigators are actively pursuing post-translational processing enzymes (e.g., Acker et al. 1987) or devising molecular biological strategies to clone them based on their activities (e.g., Eberwine et al. 1987). Once the structures of these enzymes are known, one can study their anatomical distribution, factors controlling their expression, and the way in which their activity, in turn, controls that of the opioid peptides. This would add a critical tool to the armamentarium for the study of opioids in relation to drug abuse.

Regulation of Opioid Peptides and Their Messenger RNAs

In studying any brain neurotransmitter, it is critical to examine the dynamics of the system, not simply the amounts of transmitter stored, because biological systems can rapidly compensate, quickly reestablishing an ideal equilibrium. For example, if an event, such as pain, causes neurons to secrete their opioid peptides, immediate changes in synthesis of the peptides quickly replace the depleted stores, rendering it impossible to detect a change in content or to deduce that pain has indeed led to opioid activation. In the past 3 years, many scientists have begun to rely on a combination of tools to measure dynamics; for example, measuring mRNA as an indicator of biosynthetic tone, and measuring peptides to assess content, hence obtaining a more dynamic picture of the activity of opioid systems. A number of models have been successfully used to describe these dynamics and to improve understanding of opioid functions.

A well-described anatomical loop controlling motor behavior, the nigro-striato-nigral loop, has been tested by many laboratories to elucidate the role of opioids. It should be noted that both the peptides (proenkephalin and prodynorphin products) and their receptors are highly enriched in this loop. In addition, dopamine is the primary nigro-striatal transmitter within the cells arising in the nigra and ending in striatum; numerous agonists and antagonists are available for altering dopaminergic tone. The weight of the evidence suggests that dopamine activity inhibits enkephalinergic tone in the striatum. When one removes the influence of dopamine, either by damag-

ing the cells that manufacture it (Hong et al. 1987; Vernier et al. 1988; Normand et al. 1987) or by giving the antagonist haloperidol (Romano et al. 1987; Morris et al. 1988a), there are reliable increases in enkephalin mRNA. Recent work (Morris et al. 1988b) suggests that this dopamine-induced inhibition of enkephalin in striatum may be mediated through a particular dopamine receptor, the D_2 receptor. The effects of the D_1 receptor on proenkephalin are controversial: some have found that D_1 blockade increases mRNA (Mocchetti and Costa 1987), while others have found a decrease (Morris et al. 1988b). Prodynorphin appears to have the opposite relation to dopamine in the nigro-striato-nigral loop. Dynorphin cell bodies are localized in the striatum and project to the nigra and thus bear a reciprocal anatomical relation to the dopaminergic projections (cf. Watson et al., unpublished). In the case of prodynorphin, there is no evidence of an inhibition by dopamine (Sivam et al. 1988). Rather, when a dopamine agonist is chronically administered, there is an increase in dynorphin mRNA and peptide stores, indicating a general activation of biosynthesis (Li et al. 1988).

Interestingly, administration of the stimulant amphetamine has been found to lead to similar effects on dynorphin within the nigro-striatal tract; chronic amphetamine leads to an accumulation of dynorphin stores due to an increase in biosynthesis (Trujillo et al., unpublished). Dynorphin, in turn, appears to feedback onto dopamine to inhibit its release both in the nigra (Reid et al. 1988) and in the striatum via kappa opioid receptors (Werling et al. 1988). It therefore appears that activation of dopamine in the nigro-striatal pathway leads to activation of dynorphin in the striato-nigral return path. This opioid inhibits any further release of dopamine at both ends of the loop, potentially terminating the overall activity. It should be noted that parallel, less well detailed, events appear to take place in the mesolimbic dopamine system, a system thought to be important in both reward mechanisms and schizophrenia (e.g., Werling et al. 1988; Morris et al. 1988b). This, in conjunction with the amphetamine effects, ties the dynorphinergic system with possible affective changes that precede, accompany, or result from exposure to drugs of abuse.

A second model that has received a great deal of attention is the effect of epilepsy on rodynorphin and proenkephalin mRNA in the hippocampus. Based on a variety of anatomical and biochemical tools, including measuring mRNA and quantitative peptides, as well as a variety of models—kainate lesions, electrical stimulation, and kindling—the following picture emerges: seizures or epileptiform activity in the hippocampus acutely deplete both enkephalin and dynorphin. However, dynorphin appears to be inhibited biosynthetically, as its mRNA decreases following seizures, and the peptides remain low prior to recovery, whereas proenkephalin is activated, as indicated by an increase in proenkephalin mRNA and a subsequent increase in peptide content (Gall 1988; Hong et al. 1987, 1988; Morris et al. 1988a). These profound changes in opioid peptide levels are consistent with their possible role in seizure activity, in view of the fact that electrophysiological studies show the ability of opioids to disinhibit, thus indirectly activating, granule cells in the hippocampus (Neumaier et al. 1988).

The effects of seizures on dynorphin mRNA are very rapid, becoming evident within a few hours (Morris et al. 1988a; Lason et al. 1988). This contrasts with the effect of another treatment, salt loading or dehydration, on prodynorphin mRNA in the hypothalamic-magnocellular neurons. Such treatment causes dramatic release of the co-stored vasopressin and dynorphin, resulting in a profound depletion of dynorphin content of the posterior lobe (Sherman et al. 1988b). Yet dynorphin (and vasopressin) mRNA rises over the course of several days before reaching its maximum (Sherman et al. 1986, 1988b; Lightman and Young 1987), indicating an overall activation of these neurons—that is, increased biosynthesis and release over a protracted period of time. In addition, the rate of return to normal levels, as well as reduction below normal following lowered salt levels, is quite slow, exhibiting a half-life of several days (Sherman et al. 1988b; Society for Neuroscience Meeting). It is there-

fore apparent that the same opioid precursor, for example, prodynorphin, responds to varying stimuli in different cell groups (osmotic in hypothalamus, epileptiform in hippocampus) with very different dynamics. In addition, the same stimuli (e.g., dopamine altering drugs) in the same neural network (e.g., nigro-striatonigral) can have profoundly different effects on two opioid precursors, such as prodynorphin and proenkephalin.

Finally, the regulation of POMC mRNA in the brain has not been explored as extensively. Nelson et al. (1988) have described the effect of aging on brain POMC message. Increases have been found in brain POMC mRNA upon repeated stress (Akil et al., unpublished). Interesting results have been obtained with chronic morphine, as will be described below. In contrast, numerous studies have focused on the effect of various manipulations, especially stress on pituitary POMC. The effect of repeated stress on POMC mRNA and POMC peptides stored in the anterior lobe has been described (Shiomi et al. 1986; Robinson et al. 1987), as has the nature of the peptides released following further stress (Young and Akil, unpublished). Tozawa et al. (1988) have reported on the effect of insulin stress and Dave et al. (1987) on the role of calcium in increasing POMC following activation by the secretagogue, corticotropin releasing hormone (CRH). It is not surprising that pituitary POMC is used as the ultimate model for studying the effect of stress on the dynamics of a system, as it is critical in producing the hormone ACTH, which plays a pivotal role in the organism's responsiveness to stressful stimuli.

Effect of Chronic Morphine on Endogenous Opioid Peptides and Their mRNAs

When they were discovered, several investigators examined the effects of chronic administration of morphine on the levels of endogenous opioids, with generally negative results. This failure to see changes in the brain's natural opioids when external opiates were given was surprising. Based on knowledge of other systems, one would expect the body to decrease production of its natural opiates in order to compensate for the presence of the administered morphine. There are at least two possible explanations for the failure to detect such decrements: (1) The endogenous opioids do not shut down and are therefore different from previously studied systems in the way they control transmitter levels in relation to receptor occupancy; or (2) endogenous opioid systems do shut down following chronic morphine, but there is an overall change in dynamics, so that levels do not reveal the activity in the systems. The latter hypothesis is now directly testable, thanks to the advent of molecular biological tools that permit the measurement of mRNA as described above.

To our knowledge, there is a single positive report on the effect of chronic morphine on proenkephalin mRNA in brain (Uhl et al. 1988), which describes a decrease in this message with chronic treatment, thereby supporting the idea of a decrease in activity of this precursor system. Others, however, were unsuccessful in detecting changes in proenkephalin mRNA (Mocchetti and Costa 1987).

The effect of chronic morphine on the beta-endorphin precursor POMC, in brain, is equally new. Mocchetti and Costa (1987) first reported a decrease in hypothalamic POMC mRNA after 5 days of chronic morphine administration. Others have carried out a systematic study on the effects of different periods of morphine administration on POMC mRNA and peptide levels in the brain and spinal cord (Bronstein and Akil 1989; Bronstein et al. 1988; Bronstein and Akil, unpublished). Because the beta-endorphin precursor gives rise to multiple forms of beta-endorphin, with a wide range of biological potency, possible changes in peptide forms have also been examined. Overall, in agreement with Mocchetti and Costa (1987), decreases were found in POMC mRNA following chronic morphine administration. In addition, a change was noted in the ratio of beta-endorphin forms at certain time points after chronic treatment, but not at others. In general, these results indicate that chronic morphine administration causes a shutdown in the activity of the brain beta-endorphin system and produces a transient

alteration in post-translational events leading to a differing composition of peptide stores (Bronstein et al., unpublished). The exact interplay of these various dynamic events still needs to be elucidated.

Finally, the effect of chronic opiate administration on the prodynorphin family has received surprisingly little attention. Weissman and Zamir (1987) reported an increase in dynorphin levels in accumbens and globus pallidus following 3 days of heroin treatment. Here again, studies have recently been undertaken to examine this question (Trujillo et al. 1987, Society for Neuroscience; Bronstein et al. 1988; Trujillo and Akil, unpublished). Results to date concern peptide levels and reveal significant elevations following repeated morphine administration. Interestingly, changes are seen in the two systems discussed above, in the nigro-striato-nigral loop, which controls motor behavior, and in the limbic dopamine system, which is critical in affect and reward mechanisms. However, these results cannot be interpreted in dynamic terms until studies of prodynorphin mRNA levels are completed. If mRNA levels are decreased, this would suggest a reduction in the overall activity of the dynorphinergic neurons, leading to less secretion, and accumulation of peptides in the stores. If, on the other hand, mRNA is increased, another situation will have been uncovered in which prodynorphin and proenkephalin regulations go in opposite directions.

In either case, one needs to examine what happens to the increased stores of dynorphin peptides upon opiate withdrawal. It is logical to propose that they may be actively released during that stage. As dynorphin is known to activate kappa receptors (see below), and as such activation often leads to aversive responses in animals and to dysphoria in humans (Pfeiffer et al. 1986), it is quite conceivable that this perturbation in dynorphin levels may contribute to the negative affect expressed during opiate withdrawal.

In general, a better understanding of the dynamic changes in endogenous opioids in various brain regions needs to be coupled to a mechanistic description of opiate receptor changes in order to begin to explain at the cellular level how opiate tolerance and dependence develop. Such studies have begun using a broader set of tools and should yield exciting results in the near future.

Control of Expression of Opioid Precursor Genes: The New Frontier

Study of the regulation and expression of opioid genes is becoming increasingly important, because the factors that control gene expression will determine (1) which cells in the brain or which tissues in the body will express each of the opioid precursors; (2) how much these genes will be expressed in a given cell; (3) what signals these genes will respond to from the environment of the cell in order to increase or shut down their expression; and (4) how any of these controls can be aberrant, leading to dysfunction in this system.

The tool of in situ hybridization (cf. Lewis et al. 1986; Watson et al., in press) has been extremely useful for studying cell-specific expression of opioid precursor mRNA in various brain structures. In addition, this technique has become increasingly more quantitative, permitting the study of regulation of mRNA expression at the single cell level (Herman et al., in press). A variation on this technique, termed "intronic in situ," (Fremau et al. 1986) has the potential for studying changes in the rate of gene transcription (copying into mRNA) also at the level of single cells. Finally, in situ hybridization has revealed that neurons and endocrine cells are not the only types that express opioid genes. Proenkephalin mRNA has recently been observed in a type of glial cells, the pituicytes of the posterior pituitary (Schafer et al., unpublished), and prodynorphin mRNA in the cells of the adrenal cortex that synthesize glucocorticoids (Day et al. 1988, Society for Neuroscience and 1989 Miami Biotechnology meeting). The observation of proenkephalin in pituicytes is consistent with the findings that glial cells in culture or glial cell lines can also express proenkephalin mRNA (Vilijn et al. 1988; Schwartz and Simantov 1988; Yoshikawa and Sabol 1986).

However, specific unknown factors must allow certain tissues or cells (e.g., pituitary, discrete nuclei in the brain, or pituicytes) to express these opioid precursors, while other cells keep the gene repressed. Such factors are only now beginning to be explored through the use of transgenic animals (Tremblay et al. 1988).

Beyond controlling the gene at the level of tissue-specific expression, there are numerous controllers of the rate of transcription of a gene—factors that cause a gene to be repressed or copied very actively into mRNA. Obviously, such factors are the critical controllers of the first step in the synthesis of the opioid peptides. Typically, these elements, called transacting factors, are proteins, made within the cells, which bind specific sequences of DNA on the gene and affect its transcription. In general, transacting factors respond to signals from outside the cell by being altered (e.g., activated), binding to DNA, and modifying gene expression.

The proenkephalin gene was among the first prohormones for which a specific DNA site of regulation was described. Comb et al. (1986) identified a "cyclic-AMP (cAMP) inducible element," a specific stretch of DNA that constitutes a binding site for a cAMP-sensitive transacting factor. Thus, when certain receptors on a cell are activated, they can increase the intracellular levels of cAMP (the second messenger). This, in turn, leads to a rapid change in one or more DNA binding proteins, which recognize a very specific sequence of DNA, bind to it, and lead to an increase in gene transcription. Several cAMP-responsive elements have since been identified in a number of prohormone genes, and they resemble closely the proenkephalin element. It is likely that proenkephalin is equally responsive to the other major second messenger system, which involves phospholipids and protein kinase C (Comb et al. 1986; Kley 1988). Proenkephalin, in addition, is also sensitive to the glucocorticoids, probably via the glucocorticoid receptor (GR), which itself is a DNA binding protein (i.e., a transacting factor). Although a detailed analysis of the GR responsive element in proenkephalin has not been completed, several lines of evidence suggest that proenkephalin gene expression is increased by glucocorticoids (Yoshikawa and Sabol 1986; Inturrisi et al. 1988).

The factors that modulate POMC gene expression are also being identified (cf. Lundblat and Roberts unpublished). It is clear that the secretagogue corticotropin releasing hormone (CRH) binds to receptors on the POMC-producing cells in the anterior pituitary, activates the second messenger cAMP, and leads to a cascade of events enhancing the transcription of POMC, presumably via a cAMP responsive element (Simard et al. 1986; Lundblat and Roberts 1988), which resembles the proenkephalin cAMP element. However, unlike the proenkephalin gene, the POMC gene is inhibited by glucocorticoids (Roberts et al. 1987; Eberwine et al. 1987) and this is most likely due to a negative influence of the glucocorticoid receptor onto that gene, mediated either directly through binding a distinct negative DNA element or by indirect mechanisms, whereby the glucocorticoid receptor prevents the binding of critical transcriptional factors or of enhancing factors (Charron and Drouin 1986). Finally, the regulation of the prodynorphin gene is still in the early stages of exploration. Similar strategies are being employed to examine these control elements.

SUMMARY OF OPIOID ADVANCES

This Chapter focuses on the use of molecular biological tools in the study of endogenous opioids and their precursors, mRNA and genes, as these approaches have yielded the most dramatic advances in understanding these systems. Several models of study have been identified (motor systems, stress, seizures, water balance), which are helping to uncover the "cellular logic" underlying the responses of opioids from gene to secretion. This understanding is now being extended to exploring the effects of tolerance to and dependence upon exogenous opiates on the natural ligands.

The Endogenous Opioid Receptors

The past 3 years have been a time of consolidation for opioid receptor research. The major effort of many laboratories has been aimed at uncovering the actual structures of these receptors. Although significant progress has been made, there is, to date, no published sequence of any of the opioid receptors, either at the protein or DNA levels. However, using a variety of techniques such as binding assays, bioassays, receptor autoradiography, electrophysiology biochemistry, and behavior, we continue to learn a great deal about the distribution of these receptors, the way they couple to the second messengers, the natural and synthetic opiates they recognize, and the role they play in various behaviors, including abuse of drugs.

Opioid Receptor Multiplicity and Distribution

Receptors are discussed in the plural because it is clear that there are more than one, just as there are more than one opioid peptide. Most biologists would agree on the three major types: the mu receptor, which binds morphine, the delta receptor, which prefers enkephalins, and the kappa receptor, which favors the prodynorphin products. Many would also agree that there is good evidence, in peripheral tissue, for an epsilon receptor, selective for beta-endorphin (this receptor type is hard to demonstrate in the brain). There are also numerous suggestions for other types or subtypes of receptors—for example, multiple types of kappa (Wood and Iyengar 1986; Mansour et al., unpublished) or multiple types of mu. However, these are somewhat more difficult to discern and characterize.

It should be noted that there is not a one-to-one correspondence between the multiple opioid peptide families and the multiple opioid receptors. Products from a given family can interact with more than one opioid receptor, and a given receptor can receive signals from more than one family. For example, the prodynorphin products, although kappa-preferring, can also interact with mu receptors with good affinity and, depending on their processing, with delta receptors as well. Beta-endorphin, although it may have a unique receptor, epsilon, has excellent affinity to both mu and delta sites (Akil et al. 1981; Shook et al. 1988) and the enkephalins, while delta selective can easily bind mu. In addition, a precursor can, through alternative processing, give rise to opioid peptides that run contrary to the overall pattern of that precursor. For instance, proenkephalin can be processed to peptides such as amidorphin (Liebisch et al. 1986) or BAM 18, which have mu receptor selectivity (Hurlbut et al. 1986). There is obviously a lack of rigid association between opioid peptides and particular receptor types. At any one time, the activation of an opioid circuit is determined by which opioid peptides are physically adjacent to which type(s) of opioid receptors, rather than by some theoretical rank order of preference. It is therefore critical to describe the distribution of the multiple types of opioid receptors, to distinguish them from each other, and to attempt to relate them to the distribution of opioid peptide products.

Using more selective synthetic opiate drugs, or peptide analogs that clearly distinguish mu, delta, and kappa receptors, several groups have described the distribution of opioid receptors in the brain with autoradiography (Mansour et al. 1987, 1988; Herkenham and McLean 1988; Sharif et al. 1988; Jomary et al. 1988; DeSouza et al. 1988; Hawkins et al. 1988). Although there are species differences and slight disagreements based on the use of varying paradigms, the overall picture that has emerged is remarkably consistent and should provide an excellent anatomical framework within which to conduct functional studies.

Receptor Solubilization, Purification, and Cloning Attempts

As stated above, numerous groups have devoted serious effort to the goal of isolating, sequencing, and cloning various opioid receptors. They include attempts at photo-affinity labeling (Kooper et al. 1988), affinity chromatography (Ueda et al. 1988; Maneckjee

et al. 1988), and the use of extremely high affinity ligand such as ^{125}I beta-endorphin (Keren et al. 1988). Opioid receptors have been solubilized (put in solution and stripped away from the membranes) using detergents followed by various purification tools (Demoliou-Mason and Barnard 1986; Cho et al. 1986). These solubilized proteins have been used to generate antibodies (Maneckjee et al. 1988) or to characterize the coupling to G proteins, proteins critical for second messenger functions (Wong et al. 1988). Some of these investigators believe that they have achieved extensive purification of a particular receptor type using a combination of steps such as solubilization, affinity chromatography, and lectin chromatography (Simon 1987). Several other researchers, such as J.D. Barchas at Stanford University; A. Goldstein at Stanford University; Horace Loh at the University of California, San Francisco; and O. Civelli at the University of Portland, are attempting to use molecular biological tools for expression cloning of opioid receptor types. This approach, though less tedious than protein purification, is also fraught with pitfalls. Efforts have been presented and discussed in scientific meetings, but no clones have been published to date.

Opioid Receptors Coupling and Electrophysiology

The beginning of this chapter discussed the importance of understanding not only the opioid peptides (the first messengers) and their receptors, but also the second messengers—those elements within a cell that indicate to that cell that the receptor has been activated and lead to an internal cascade of events, resulting in continued communication with yet other cells. Until recently, identifying the biochemical second messengers to which brain opioid receptors were coupled has been elusive. When opioid receptors are expressed in tumor lines, it is relatively easy to show their effects on a particular second messenger pathway, the adenylate cyclase system (Puttfarcken et al. 1988), but such an effect is extremely difficult to detect in the central nervous system (Childers 1988), suggesting that the coupling in tumor lines either represents an aberrant phenomenon or is due to the expression of somewhat unusual subtypes of opioid receptors.

Although classical biochemical approaches have failed to uncover the brain's opioid receptors second messengers, electrophysiological studies have been very informative. The work of several groups, including those led by R.A. North and R.L. MacDonald, has clearly established that opioid receptors modulate ion fluxes across cell membranes. North and colleagues (1987) have demonstrated that both mu and delta receptors belong to a family of neurotransmitter receptors that increase potassium conductance, leading to hyperpolarization, and thus appear to modulate potassium channels. The work of MacDonald and his colleagues has focused on the specific coupling of kappa receptors with another ion channel, the calcium channel, modulating particularly the so-called N currents (MacDonald and Wertz 1986; Wertz et al. 1987; Gross and MacDonald 1987). How do these receptors control the state of channels, which are themselves membrane proteins? Do they do so via an intermediary protein, or are they physically connected? Recent work shows that the coupling takes place via special proteins termed G proteins, which interface the receptors with the channel (North et al. 1987). Yet a classical second messenger (e.g., cAMP) does not appear to be a necessary intermediate in this modulation of channels (North et al. 1987). Thus, the opiate receptors are part of a growing family of receptors that use the mechanisms of effector coupling, giving a somewhat different type of second message. Interestingly, the electrophysiological results converge with other evidence in suggesting a particular structure for these receptor proteins—the so-called seven-transmembrane domain family to which G protein coupled receptors belong. Furthermore, these effector mechanisms have proven to be an important clue in investigating mechanisms of morphine tolerance.

Opioid Receptors and Opiate Tolerance and Dependence

Binding studies continue to be used to examine the effect of repeated morphine (or other opiate drug) administration on the affinity and numbers of receptor types. As more selective ligands become available, it is reasonable to return to this question with better tools. Interestingly, such studies appear to have led to the detection of changes following chronic opiate treatment, which had been difficult to discern in the past. A majority of investigators report a down-regulation of mu receptors following chronic opiate treatment in the neonate (Tempel et al. 1988) as well as in the adult rat (Rogers and El-Fakahany 1986; Tao et al. 1987) and in a mu-expressing cell line (Puttfarcken et al. 1988), although one group has obtained conflicting results (Rothman et al. 1987). Interestingly, one study has shown a difference between the effects of heroin and morphine on mu-opiate receptor activity (Bolger et al. 1988), suggesting that tolerance development to all opiate drugs may not proceed in the same way. Although these findings are encouraging, they may not address the central phenomenon in opiate tolerance development—i.e., a loss in efficacy. In other words, even when opiates do bind to the receptors of tolerant animals, they do not produce the consequences on the cell that one would see in a normal animal. This may be because the receptor is no longer physically located on the outer membrane in a position that allows it to modulate channels. Evidence of increase in mu receptor internalization following exposure to morphine has indeed been obtained in cell lines (Puttfarcken et al. 1988). Alternatively, the receptor protein itself may be modified in a subtle way (such as by addition of phosphate groups), rendering it less able to couple to the G protein. Indeed, electrophysiological studies point in that direction. They show that the mu receptors of the tolerant rat, located in the locus coerulus, are less able to increase potassium conductance, which is a main effect in the normal animal (Christie et al. 1987). The study went on to show that this is not due to a change in the properties of the potassium channel itself (it responded normally to modulation by alpha$_2$ adrenergic receptors); nor was it due to a change in the affinity of mu receptor binding to opiates, suggesting, by elimination, a change at the level of the receptor coupling to the channel, presumably via the G protein (Christie et al. 1987).

Thus, we are beginning to piece together a more dynamic picture of changes occurring during tolerance, both at the opioid receptor and peptide levels. Relatively less is understood about the cellular mechanisms of physical dependence. A working model used by many continues to be that the total opioid system becomes less efficient at almost every level during chronic opiate administration, thus counteracting the artificially large amounts of opiates present in the body. When opiates are withdrawn, the brain is left with a system that has been "turned off"—there is less peptide synthesis, there are no efficacious receptors, and there is no help from artificial opiates. As a consequence, the symptoms of withdrawal take place and continue until a new biochemical equilibrium is reestablished. This view, though broadly accurate, is also likely to be simplistic, considering the number of opioid peptides and receptors at play, in various brain structures, as well as the likely consequences of opiate and other brain systems beyond the opioids themselves. Nevertheless, the recent advancements in understanding tolerance-related phenomena are likely to pave the way to a better understanding of mechanisms of physical dependence.

FUTURE DIRECTIONS

It is evident from the above discussion that the past 3 years of basic research have enriched knowledge of the function and regulation of the naturally occurring opioids and their receptors. It is also clear that the introduction of molecular biological tools to this field has expanded horizons, in both the structural and the functional domains. The most obvious challenge ahead is to define the structure of opioid receptors, either through protein purification methods or through cloning strategies. This will allow scientists to deter-

mine the number of receptors, their pharmacological specificities, their interactions with natural peptides or opiate alkaloids, and the process by which they couple to second messengers. A second major area of growth is the elucidation of the enzymes involved in the synthesis and processing of the peptides. If these are specific, they may provide an excellent target for designing new drugs that modulate the synthesis of natural opioids so as to increase or decrease the tone of the system (i.e., make more of the inherent naturally occurring endorphins for pain relief, rather than rely on external sources).

Clearly, however, the ultimate challenge is to understand the basis of individual differences, as such differences are important in determining why certain individuals are more likely to seek and become addicted to opiates and other drugs of abuse. Conceivably, some of the diversity may be structural; for example, there may be actual physical differences in the receptors. However, it is more likely that the range of variability can be explained by differences in the ways that these systems respond to stimuli such as pain, stress, and reward, or in how they adjust when external drugs are given. Other differences may revolve around the interactions between opioids and other neural systems, leading to a different "tuning" of the systems involved in mood, affect, reward, and physical or emotional pain. All the elements of these opioid systems, and their regulation and interaction with other systems, must be understood, and their variability investigated, in order to arrive at rational and mechanistic models of the biology underlying drug abuse.

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☆ U.S.GOVERNMENT PRINTING OFFICE:1991-281-820/44104

DHHS Publication No.(ADM)91-1704
Printed 1991